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Guidelines for Evaluating Chronic Cough in Pediatrics

ACCP Evidence-Based Clinical Practice Guidelines

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Objectives: **To review relevant literature and present evidence-based guidelines to assist general and specialist medical practitioners in the evaluation and management of children who present with chronic cough.**

Methodology: **The Cochrane, MEDLINE, and EMBASE databases, review articles, and reference lists of relevant articles were searched and reviewed by a single author. The date of the last comprehensive search was December 5, 2003, and that of the Cochrane database was November 7, 2004. The authors' own databases and expertise identified additional articles.**

Results/conclusions: **Pediatric chronic cough (*ie*, cough in children aged < 15 years) is defined as a daily cough lasting for > 4 weeks. This time frame was chosen based on the natural history of URTIs in children and differs from the definition of chronic cough in adults. In this guideline, only chronic cough will be discussed. Chronic cough is subdivided into specific cough (*ie*, cough associated with other symptoms and signs suggestive of an associated or underlying problem) and nonspecific cough (*ie*, dry cough in the absence of an identifiable respiratory disease of known etiology). The majority of this section focuses on nonspecific cough, as specific cough encompasses the entire spectrum of pediatric pulmonology. A review of the literature revealed few randomized controlled trials for treatment of nonspecific cough. Management guidelines are summarized in two pathways. Recommendations are derived from a systematic review of the literature and were integrated with expert opinion. They are a general guideline only, do not substitute for sound clinical judgment, and are not intended to be used as a protocol for the management of all children with a coughing illness. Children (aged < 15 years) with cough should be managed according to child-specific guidelines, which differ from those for adults as the etiologic factors and treatments for children are sometimes different from those for adults. Cough in children should be treated based on etiology, and there is no evidence for using medications for the symptomatic relief of cough. If medications are used, it is imperative that the children are followed up and therapy with the medications stopped if there is no effect on the cough within an expected time frame. An evaluation of the time to response is important. Irrespective of diagnosis, environmental influences and parental expectations should be discussed and managed accordingly. Cough often impacts the quality of life of both children and parents, and the exploration of parental expectations and fears is often valuable in the management of cough in children.** ***(CHEST 2006; 129:260S–283S)***

Key words: asthma; children; cough; evidence-based medicine; guideline; treatment

Abbreviations: ACE = angiotensin-converting enzyme; AHR = airway hyperresponsiveness; ARI = acute respiratory infection; ETS = exposure to tobacco smoke; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; HRCT = high-resolution chest CT; ICS = inhaled corticosteroid; NO = nitric oxide; OTC = over the counter; RCT = randomized controlled trial; URTI = upper respiratory tract infection

Clinicians specializing in children's health are well aware of the limitations and possible adversity in the extrapolation of data from adults to children.[1,2] Child-specific guidelines are differentiated from those for adults in common respiratory diseases such as community-acquired pneumonia[3–5] and asthma.[6] However, rigidity in the adherence to child-specific data may also be disadvantageous to children, given

the relative paucity in pediatric research in comparison to research in adults.[1] In the area of cough, there are similarities but also clear clinical and physiologic differences between children and adults. Some adult definitions (*eg*, chronic bronchitis and COPD are not recognized diagnostic entities in the pediatric respiratory literature and main textbooks[7,8]) are inappropriate for children. Etiologic differences and frequency etiologies associated with cough are also evident from the literature.[9–11] Furthermore, adults and children also have different responses to some medications (*eg*, first-generation antihistamines that are efficacious for treating cough in adults are not only not beneficial in children when the evidence is critically evaluated,[12,13] but their use is also associated with more morbidity[14,15] in children when compared to adults). Personal and institutional practice may well differ from the evidence reviewed and presented in this article. This review is focused on chronic cough, and the data are limited to children unless specifically stated. Although the cutoff age for pediatric care in the United States is 18 years, we have chosen a lower cutoff age here (*ie*, 14 years of age) based on the limited evidence in the cough literature that adolescents are more like adults (*eg*, the response to over-the-counter (OTC) medications for cough as summarized in a Cochrane review[16]).

The Cochrane, MEDLINE, and EMBASE databases, review articles, and reference lists of relevant articles were searched and reviewed by a single author. All recommendations were based on the pediatric literature and current evidence, and were accepted by the panel on December 5, 2004.

Defining Cough in Children

Cough can be defined based on time frame (*ie*, duration of cough), quality (*eg*, dry or wet,[17] brassy, or staccato), or suggested etiology (*ie*, specific and nonspecific).[11] The majority of the terms defined below have been used in various publications.[11,18,19] The background for justification of the use of these terms has been reviewed elsewhere.[20] Chronic cough in children is defined as a cough of > 4 weeks duration based on the current data of cough related to acute upper respiratory infections in children.[21,22] This review and the evidence presented are also focused on nonspecific chronic cough (*ie*, cough in the absence of symptoms outlined in Table 1) as data on specific cough would encompass the entire spectrum of pediatric respiratory disease.

Clinical History, Examination, and Investigations

There is a general lack of data on the specificity and sensitivity of individual symptoms when evaluating cough in children. Furthermore, other than the validity of using dry/wet cough and brassy/nonbrassy in children,[17] there are few data on the validity of other cough characteristics and/or clinical examination. There are also only case series or cohort data relating to the value of available investigations for the evaluation of chronic cough in children. The data are summarized in Table 2.[66,73,74,79,80,88,89,94,103,105,106,117,252–261] As chronic cough can be associated with significant consequences (*eg*, a retained foreign body causing bronchiectasis), each child with chronic cough should be thoroughly reviewed and when appropriate relevant investigations should be performed. Clearly, the extent of investigations should be based on the clinical setting, population examined, and available expertise. Adverse events to investigations must be considered as, in children, some investigations such as CT scans have a higher risk from radiation and general anesthesia (if required) when compared with adults.

Etiologic Associations

Some of these aspects have been reviewed previously[9,23–25] and limited new data are presented (Table 3[9,89,94,103–105,175,177,262–264]) due to space limitations. Unlike adult data, the relationship between cough and upper airways disorders, asthma, gastroesophageal reflux disease (GERD) [as well as the frequency of these disorders] is less convincing in children. Other considerations for the etiology of nonspecific cough include the inhalation of a foreign body, airway lesions, environmental pulmonary toxicants, nonasthmatic eosinophilic bronchitis (poorly described in the pediatric literature), respiratory infections and postinfectious cough, the side effects of medications, and otogenic causes.

Evidence-Based Treatment

Based on the current knowledge of the large placebo effect seen in cough studies and shown in all randomized controlled trials (RCTs) in children,[12,13,26] data based on cohort studies must be interpreted with caution. Furthermore, the report-

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Table 1—*Pointers to the Presence of Specific Cough*

Abnormality	Examples of Etiology
Auscultatory findings	Wheeze-intrathoracic airway lesions (*eg*, tracheomalacia, asthma); crepitations, any airway lesions (from secretions), or parenchyma disease such as interstitial disease
Cardiac abnormalities	Associated airway abnormalities, cardiac failure
Chest pain	Arrhythmia, asthma
Dyspnea or tachypnea	Any pulmonary airway or parenchymal disease
Chest wall deformity	Any pulmonary airway or parenchymal disease
Digital clubbing	Suppurative lung disease
Daily moist or productive cough	Suppurative lung disease
Exertional dyspnea	Any airway or parenchymal disease
Failure to thrive	Any serious systemic including pulmonary illness such as cystic fibrosis
Feeding difficulties	Any serious systemic including pulmonary illness, aspiration
Hemoptysis	Suppurative lung disease, vascular abnormalities
Hypoxia/cyanosis	Any airway or parenchyma disease, cardiac disease
Immune deficiency	Suppurative lung disease or atypical infection
Neurodevelopmental abnormality	Aspiration lung disease
Recurrent pneumonia	Immunodeficiency, atypical infections, suppurative lung disease, congenital lung abnormalities, trachea-esophageal H fistulas

ing of cough is biased,[27] and Hutton et al[28] described the fact that "parents who wanted medicine at the initial visit reported more improvement at follow-up, regardless of whether the child received drug, placebo, or no treatment."

In general, the management of specific cough should be based on etiology. When the underlying condition or exacerbating factor is managed, cough subsequently resolves. For example, the severity and frequency of wet cough resolves following the management of an acute exacerbation of chronic suppurative lung disease. The management of specific cough encompasses the entire spectrum of pediatric pulmonology, which is well beyond the scope of this article. (A guideline for nonspecific cough, with its limited evidence, is presented in Figures 2 and 3, and the evidence is presented in the text and summarized in Table 4[12–16,74,75,79,90,91,122,207,208,211,215,225–227,231–233,237,265–271].) Irrespective of the cause of cough, particular attention to tobacco smoke exposure as well as parental expectations and concerns are advised, based on data on acute upper respiratory infections. When appropriate and when no pediatric data exist, readers are referred to the adult guideline, but this extrapolation should be cautiously accepted. If a trial of medications is warranted, "time response" (Table 4) should be considered, the child's case should be reviewed within the relevant time frame, and therapy with medications should be stopped when appropriate.

Introduction and Background

In the management of illnesses in children, the extrapolation of adult-based data to children can sometimes result in unfavorable consequences.[1,2,29] The pattern of respiratory illness in children is clearly different from that in adults; for example, viruses associated with the common cold in adults can cause serious respiratory illnesses such as bronchiolitis and croup in previously well young children.[30] Thus, it is not surprising that pediatric-specific guidelines exist for children in the management of common illnesses such as asthma,[6] GERD,[31] and community-acquired pneumonia.[3–5]

The physiology of the respiratory system in children is similar to that in adults in many ways. However, there are also distinct differences between young children and adults, including maturational differences in airway, respiratory muscle, and chest wall structure, sleep-related characteristics, respiratory reflexes, and respiratory control.[32–34] In the physiology of cough, gender differences in cough sensitivity that are well-recognized in adults[35] are absent in children.[36] In children, cough sensitivity is instead influenced by airway caliber (*ie*, FEV_1) and age.[36] the plasticity or adaptability of the cough reflex has been shown in animals,[37] and one can speculate that there are also maturational differences in the cough reflex.[38] In young children, the medical history is limited to parental perception and availability. The combination of these factors results in variations in differential diagnoses. As an example, the unknown inhalation of a foreign body (delayed diagnosis can result in permanent lung damage[39]) is not uncommon in children; the frequency of acute upper respiratory tract infections (URTIs) is age-related; studies from the 1940s to the 1960s have shown that children have 5 to 8 acute respiratory infection (ARI) episodes per year,[40] while in more recent studies[41] children aged < 5 years have 3.8 to

Table 2—*Summary of Studies That Described the Yield of Specific Investigations for Cough in Children

Study	Indication and Study Population	Key Findings and Authors' Conclusion	Additional Points or Limitations of Study/Test
Chest CT scans			
Coren et al[252]	Case series, chronic productive cough, tertiary hospital	Yield, 43%, where bronchiectasis was documented	Yield of CT scan in the evaluation of isolated cough without the presence of specific cough pointers (Table 1) is unknown
Sinus CT scans			
Tatli et al[253]	Case series, chronic cough, otolaryngology clinic	66% abnormal, but rhinorrhea, nasal congestion, sniffling, and postnasal drip had no significant relationship with paranasal sinus CT scan abnormality	50% asymptomatic children have incidental sinus abnormality[254]; poor concordance in diagnostic modalities[117]
Flexible bronchoscopy			
Callahan[88]	Case series, chronic cough, private clinic	Bronchoscopy assisted in the diagnosis in five (5.3%) children	
Thomson et al[89]	Case series, chronic cough, tertiary center	Airway abnormalities (mainly tracheobronchomalacia) present in 46%	Unknown cause and effect
Airway fluid/lavage and cellular assessment			
Fitch et al[105]	Case series, untreated persistent cough	3 of 23 children had asthma-type airway inflammation	
Zimmerman et al[94]	Case series, post infectious cough, treated and untreated asthmatic patients, tertiary hospital	6 of 11 children with post infectious cough had AHR, but airway eosinophils and eosinophil cationic protein were normal	
Gibson et al[103]	Cohort, community study; four groups (wheeze, cough, recurrent chest colds, control subjects)	"Persistent cough and recurrent chest colds without wheeze should not be considered a variant of asthma"	
Marguet et al[106]	5 groups: asthma, chronic cough, infantile wheeze, cystic fibrosis, and control	"Chronic cough is not associated with the cell profiles suggestive of asthma and in isolation should not be treated with prophylactic antiasthma drugs"	
Kim et al[255]	Cohort, "cough-variant asthma"	> 2.5% eosinophils in sputum were more likely to have classical asthma on follow-up	No control group
Colombo and Hallberg[256]	Evaluation of lipid-laden macrophage index as an indicator of aspiration as a cause of chronic cough		Increased lipid-laden macrophages index is found in other lung diseases in the absence of aspiration[257–259]; useful supportive but not diagnostic evidence
Airway hyperresponsiveness			
Chang et al[74]	RCT, chronic cough	AHR unpredictive of efficacy of inhaled salbutamol and corticosteroids (400 μg beclomethasone/d) for cough frequency or cough sensitivity in children with recurrent cough	Older studies on AHR mentioned in text
Strauch et al[260]	Cohort, community study	AHR associated with wheeze and dyspnea but not associated with dry cough or nocturnal cough once confounders were accounted for	
Galvez et al[73]	Case series, mixture of children and adults	Some had spirometric evidence of obstructive airways before AHR (FEV_1, 62%); 97% of AHR-positive subjects improved after asthma Rx; 87% of AHR-negative subjects also improved after asthma Rx	
Spirometry			
Hannaway and Hopper[80]	Chronic cough, hospital	12 of 20 children (60%) who performed spirometry had abnormalities	Spirometry is relatively insensitive[66,261]
	Chronic cough, hospital	6 of 8 children who had spirometry had $FEV_1 < 85\%$[79]	
Thomson et al[89]	Spirometry results were normal in all able to perform the test	Normal spirogram finding does not exclude underlying respiratory abnormalities	

*Rx = treatment.

Table 3—*Additional Studies Since Review[9] That Specifically Examined the Relationship Between Cough and Asthma, and Between Chronic Cough and Infections in Children*

Study	Indication and Study Population	Key Findings and Authors' Conclusion	Additional Points or Limitations of Study/Test
Asthma			
Thomson et al[89]	Case series, chronic cough, tertiary center (n = 49)	None had asthma as the sole final diagnosis; asthma was coexistent in 2 but cough was not related to asthma.	
Faniran et al[104]	Community-based study, chronic cough (n = 1,178)	"Cough variant asthma is probably a misnomer for most children in the community who have persistent cough"	See also studies[94,103,105,105] in Table 2
Infections			
Senzilet et al[262]	Adolescents and adults with cough of 7–56 days duration (n = 442)	20% had either laboratory confirmed or laboratory evidence of pertussis	
Hallander et al[177]	Prospective vaccine study—children (aged 3–34 mo) tested (*Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Bordetella parapertussis*, and *Bordetella pertussis*) if the child or household member coughed for > 7 d	115 etiologic agents were identified in 64% of episodes (99/155) with cough for < 100 d; most common single agent was *B pertussis* in 56% (64/115), with a median cough period of 51 d, followed by *M pneumoniae* in 26% (30/115), mean cough period of 23 days, *C pneumoniae* in 17% (19/115), 26 d, and *B parapertussis* in 2% (2/115)[177]	Other microbial studies were not done, and other possible etiologies of cough were not considered; a factor that needs to be considered when analyzing such results is determining whether the infectious agent isolated is the cause of the cough[263]
Tozzi et al[175]	Prospective study in children < 6 years of age	Median duration of cough in unvaccinated (for pertussis) children was 52–61 d, that for vaccinated children was 29–39 d; respective median duration of spasmodic cough was 20–45 d and 14–29 d[175]	In children who received the acellular pertussis vaccination, pertussis infection is clinically difficult to distinguish from diseases associated with coughing caused by *B parapertussis* and other viral or bacterial infections[264]

5 infections per person per year and adults have only 2. Respiratory tract carcinomas, which are not uncommon in adults, are very rare in children, and radiation from high-resolution CT (HRCT) scans of the chest in children carry higher risks.[42] While cough may be a manifestation of asthma in both adults and children, other common causes of cough and respiratory diseases in adults such as chronic bronchitis[43] and COPD are not recognized diagnostic entities in the pediatric respiratory literature and textbooks.[7,8] Thus, the management of childhood cough should be distinguished from that of adult cough, and it mandates a separate guideline that focuses on cough in children that is relevant to children < 15 years of age. This guideline, which is applicable in more affluent countries like the United States, the United Kingdom, and Australia, requires appropriate adaptations in other population settings[44] such as in Native American[45] and Australian[19] aboriginal communities in which bronchiectasis is relatively common (*ie*, 147 to 200 cases per 10,000 children).

Pediatric cough can be classified in several ways, including those based on etiology,[23] time frame,[11] characteristics (*eg*, moist vs dry),[17] and specific and nonspecific cough (Fig 1) with a degree of overlap. The definition of chronic cough in children, however, varies from 3 weeks[46,47] to 12 weeks in duration.[11,48] There are no studies that have clearly defined when cough should be defined as chronic or persistent. A systematic review[22] showed that cough related to an acute URTI resolves within 1 to 3 weeks in most children. A prospective cohort study[21] by the same group conducted in preschool children presenting to primary care showed that 10% of children were still coughing 25 days after a URTI. They did not describe whether those children with prolonged cough had complications of URTI such as pneumonia or bacterial bronchitis. Based on the natural history of URTIs and differences between adults and children, we define pediatric chronic cough as a daily cough lasting for > 4 weeks. In this guideline, only chronic cough will be discussed and its management summarized in two pathways (Fig 2, 3).

When considering cough in children, clinicians should be cognizant of some general issues, which

Table 4—*Summary of Therapies Used for Nonspecific Cough as Reported in Literature Based on Controlled Trials*

Therapy	Time to Response*	Level of Evidence	Data Limitation and Considerations
Antihistamines			
Chronic cough	1 wk	RCTs[265,266]	Adverse events,[13–15]; inconclusive data
Acute cough	Not relevant	Systematic review,[12] RCT[13]	Nonbeneficial
Antimicrobials	1–2 wk	Systematic reviews,[227] RCTs[225,226]	Some benefit, adverse events, cost/benefit ratio[267]
Asthma type therapy			
Cromones	2 wk	Systematic review[215]	Single open trial only[268]
Anticholinergics	No data	Systematic review[211]	No trials in children
Inhaled corticosteroids	2–4 wk	RCTs[74,90]	Small benefit if any, adverse event
Oral corticosteroids		No data	No RCTs, adverse events
β_2-agonist (oral or inhaled)	Not relevant	Systematic review,[210] RCT[74]	Non beneficial[74,91]; adverse events[91]
Theophylline	1–2 wk	Observational studies[75,79,80]	No RCTs, adverse events
Leukotriene receptor antagonist		No data	No trials in children
GERD therapy			
Motility agents	Not relevant	Single controlled trial[233]	No benefit, adverse events; systematic reviews on cisapride[269] and metoclopramide[237] showed no benefit for GER but cough was not an outcome measure
Acid suppression		No data	No RCT on proton pump inhibitors, adverse events
Food-thickening or antireflux formula	1 wk	Systematic review,[237] RCTs[231,232]	Inconclusive data; one reported increase in cough[231] and a second reduction[232]
Head positioning	Not relevant	Systematic review[237]	No benefit, systematic showed no benefit for GER, and cough was not an outcome measure[269]
Fundoplication		No data	No RCT, adverse events
Herbal antitussive therapy		No data	No RCTs
Nasal therapy			
Nasal steroids	1–2 wk	RCT[122]	Mainly adults and older children (> 12 yr of age) in RCT, beneficial when combined with antibiotics for sinusitis[270,271]
Other nasal sprays		No data	No RCT, adverse events
OTC cough medications	Not relevant	Systematic review,[12,16] RCT[13]	Non beneficial, adverse events[207,208]
Other therapies			
Steam, vapor, rubs		No data	No RCTs, adverse events (*eg*, burns)

*Time to response = expected reduction in cough severity if treatment is effective, as reported by trialists; No data = no pediatric data.

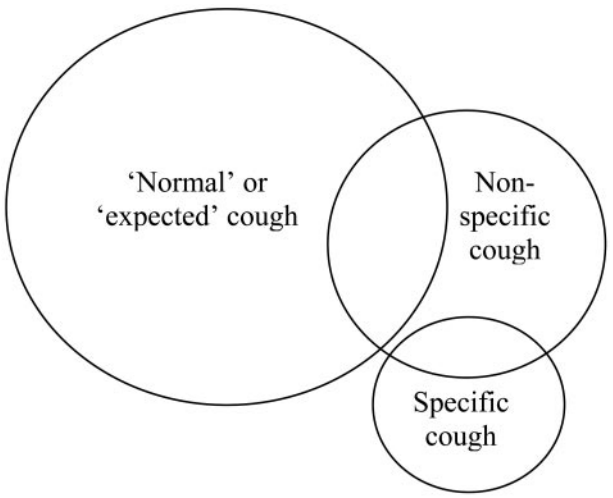

FIGURE 1. Classification of types of cough in children. The figure was reproduced from the article by Chang.[272]

are listed below. The limitations on subjective cough reporting have led to the advocacy for and development of objective measurements of cough in research circles.[27,49–51]

1. "Normal" children occasionally cough as has been described by two studies[52,53] that objectively measured cough frequency. The "medicalization" of an otherwise common symptom can foster exaggerated anxiety about perceived disease, and lead to unnecessary medical product delivery and services.[54] Cough in this situation is termed *expected cough*.
2. Questions about isolated cough are largely poorly reproducible,[55] and nocturnal cough in children is unreliably reported.[56,57] The κ value relating the chance-corrected agreement between answers to questions on cough ranges

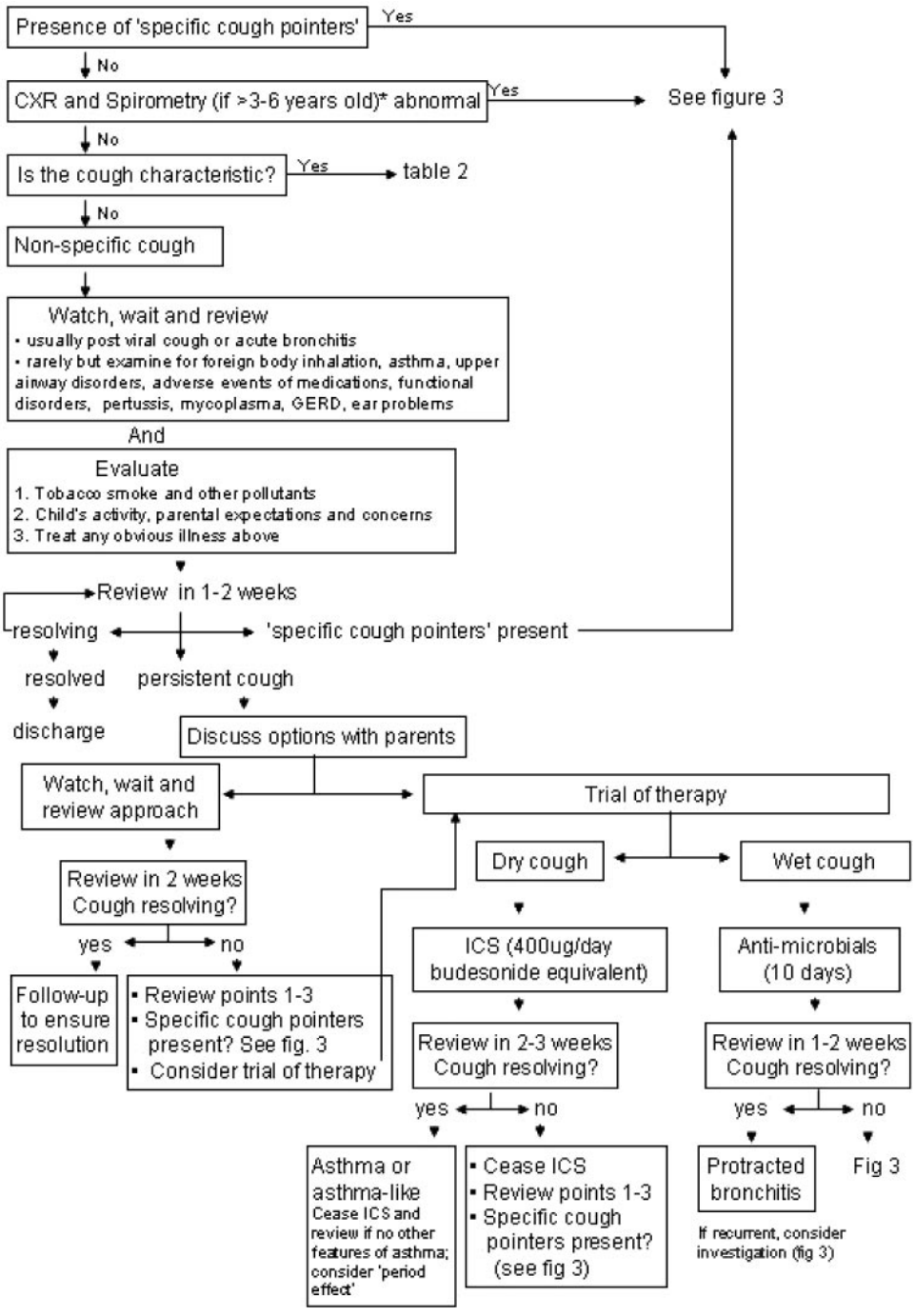

FIGURE 2. Approach to a child < 15 years of age with chronic cough. There are limitations to the algorithm, which should be read with the accompanying text. Spirometry can usually be reliably performed in children > 6 years of age and in some children > 3 years of age if trained pediatric personnel are present.[81] CXR = chest radiograph.

widely from 0.02 to 0.57.[27,55,58] In contrast, questions about isolated wheezing and asthma attacks are highly reproducible with κ values of 0.7 to 1.0.[55]

3. Cough is subjected to the period effect (*ie*, the spontaneous resolution of cough).[59] The therapeutic benefit of placebo treatment for cough has been reported to be as high as 85%.[60] The results of nonplacebo controlled intervention studies must be interpreted with caution.
4. In older children, cough is also subjected to psychological influences[61,62] because, as in

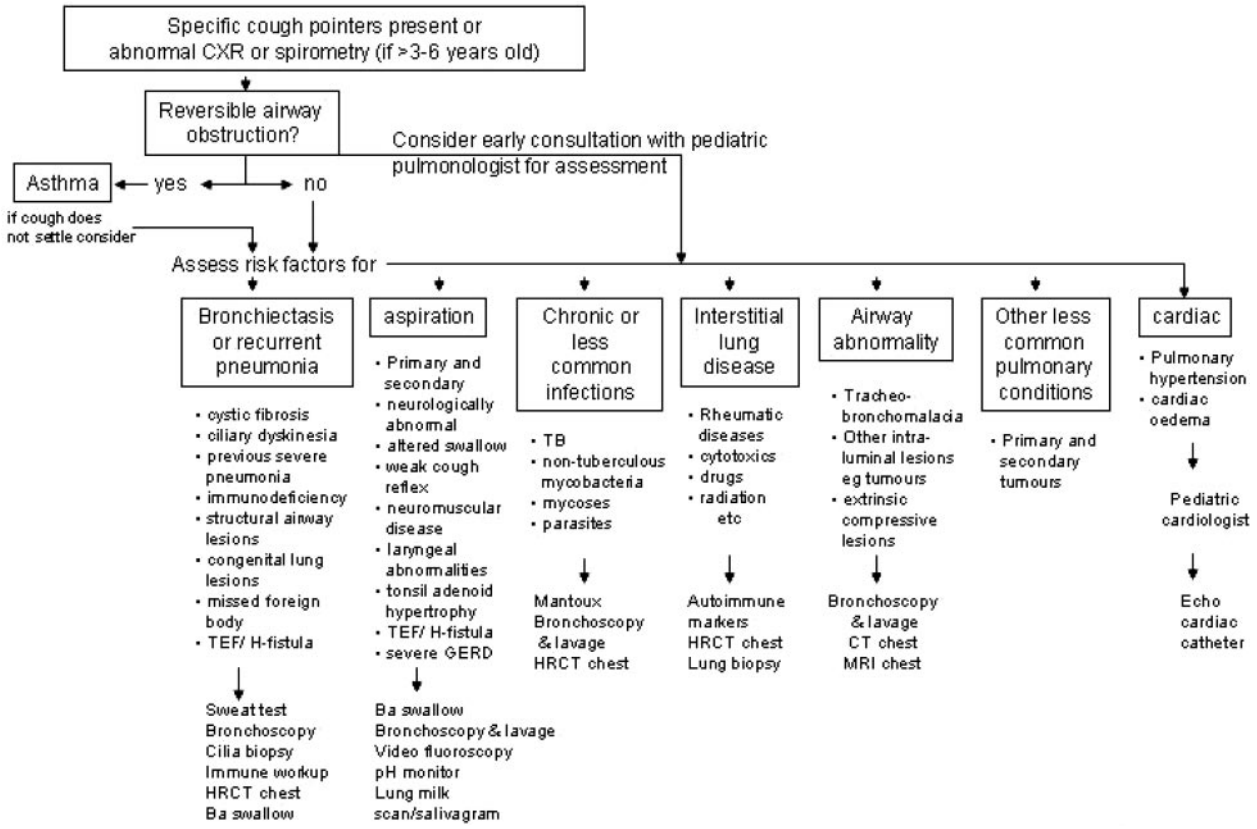

FIGURE 3. Approach to a child ≤ 14 years of age with chronic specific cough (*ie*, cough associated with other features suggestive of an underlying pulmonary and/or systemic abnormality). Children > 14 years of age should be managed as outlined in adult guidelines, but there is no good evidence concerning where the age cutoff for treatment should be. TB = tuberculosis; TEF = tracheoesophageal fistula.

adults, cough is cortically modulated.[9] Rietveld and colleagues[61,63] showed that children were more likely to cough under certain psychological settings.

5. The subjective perception of cough severity is dependent on the population that is being studied.[53] The reporting of childhood respiratory symptoms is biased, and parental perceptions of childhood cough play an important role.[27,28]

LITERATURE REVIEW OF RECOMMENDATIONS

To develop an evidence-based guideline, the following search strategy was utilized. Articles on diagnosis, etiology, treatment, and complications were searched separately. Articles published in the English language between January 1966 and December 2003 were identified from The Cochrane Register of Controlled Trials (CENTRAL), PubMed (1966 to December 2003), EMBASE (from 1997 to 2003), the list of references in relevant publications, and the authors' collection of references. The search strategy is presented in Table 5. A single author reviewed all abstracts identified from the search, and relevant articles were retrieved for full review. The searches were performed between September 1 and December 5, 2003. A final search of the Cochrane database only was conducted on November 7, 2004, using the search term "cough and children." All data presented are restricted to pediatric studies unless otherwise stated.

CHRONIC COUGH

The definition of chronic cough is a cough of > 4 weeks duration.

INVESTIGATING CHILDREN WITH CHRONIC COUGH: DIAGNOSTIC APPROACHES

Medical History and Physical Examination

Chronic cough in children secondary to respiratory diseases such as suppurative lung disease[19] and interstitial disease usually have a variety of other

Table 5—*Search strategy used*

ACE inhibitors and cough and children
Acute cough and children
Air pollution and trials and cough and children
Air pollution, randomized controlled study and children
Allergic cough and children
Allergy and chronic cough and children
Antihistamine and cough and children
Bronchoscopy and cough and children
Chronic cough and β-agonist and children
Chronic cough and children
Converting enzymes and cough and children
Cough and children
Cough guideline and children
CT scan and cough and children
Ear and cough
Education and cough and children
Eosinophilic bronchitis and children
GER and cough and children
Moist cough and children
Persistent cough and β-agonist and children
Pertussis and cough and children
Pertussis and cough and epidemiology
Pollution and cessation and cough
Pollution and cessation and cough and children
Postbronchiolitis and children
Postbronchiolitis cough and children
Postviral cough and children
Productive cough and children
Smoke and cessation and cough and children
Subacute cough and children
Treatment and cough and children
Vocal tics and children
Vocal tics and cough and children

Table 6—*Traditional Recognizable Cough in Children*

Cough Characteristic	Suggested Underlying Etiology or Contributing Factor
Barking or brassy cough	Croup,[247] tracheomalacia,[17,137,139] habit cough[62,184]
Cough productive of casts	Plastic bronchitis[248]
Honking	Psychogenic[249]
Paroxysmal (with/without whoop)	Pertussis and parapertussis[177,250]
Staccato	Chlamydia in infants[251]

specific clinical symptoms and signs.[64] However, a review of the medical literature found no reports on the specificity and sensitivity of these signs and symptoms. Based on expert opinion, children with chronic cough need to be carefully evaluated for the following:

- Symptoms and signs of an underlying respiratory or systemic disease (termed *specific pointers*) [Table 1]. When any of these symptoms and signs are present, the cough is referred to as *specific cough*.
- In some children, the quality of cough is recognizable and suggestive of a specific etiology (Table 6[17,62,137,139,177,184,247–251]). This significantly differs from the situation in adults in whom detailed questioning about the characteristics of cough was not diagnostically useful.[65] However, most of these cough characteristics recognized by pediatricians as "classical" or "traditional" have not been formally examined (*ie*, sensitivity and specificity are undefined). Of the cough characteristics presented in Table 6, only that of brassy cough has been formally evaluated.[17] The sensitivity and specificity for brassy cough (*ie*, for tracheomalacia) were 0.57 and 0.81, respectively.[17] The κ score for both intraobserver and interobserver clinician agreement for brassy cough was 0.79 (95% confidence interval, 0.73 to 0.86).[17]
- Possible exacerbating factors (see below) should also be evaluated, irrespective of the underlying etiology.

Investigations

Chronic productive purulent cough is always pathologic, and the workup usually involves detailed investigations that include the spectrum of available investigations (*eg*, chest HRCT scan), bronchoscopy, video fluoroscopic evaluation of swallowing, echocardiography, complex sleep polysomnography, and nuclear medicine scans. Determining the role of specific tests for the evaluation of lung disease is beyond the scope of this guideline because it would encompass the entire spectrum of pediatric respiratory illness. Table 2 outlines a summary of the available data when the yield (with significant abnormalities present) of tests used to investigate chronic cough were recorded.

Use of Chest and Sinus CT Scans

The chest HRCT scan is the current "gold standard" for evaluating small airway structural integrity and is more sensitive than spirometric indexes.[19,66,67] The utility of CT scans has to be balanced with the reported increased lifetime cancer mortality risk, which is age-dependent and dose-dependent. Although the risk is relatively negligible, children have 10 times the increased risk compared to middle-aged adults.[42] For a single CT scan examination of 200 mA, the lifetime attributable cancer mortality risk is 1 in 1,000 to 2,500 for a 2.5-year-old child.[42] Thus, while chest CT scans and, to a much lesser extent, sinus CT scans have definite roles in the evaluation of a child with cough, these should be uncommonly performed unless other symptoms are present. As radiation exposure and indications for conventional,

spiral, and HRCT chest scans are different and are dependent on the type of suspected lesion, prior consultation with a pediatric pulmonologist is recommended.

Flexible Bronchoscopy

Indications for flexible bronchoscopy in children with chronic cough include the following: (1) suspicion of airway abnormality, (2) localized radiology changes, (3) suspicion of an inhaled foreign body, (4) evaluation of aspiration lung disease and, (5) microbiological studies and lavage. In a European series,[68] chronic cough was the indication for 11.6% of the 1,233 pediatric bronchoscopies performed. Utility for flexible bronchoscopy is dependent on the child's medical history and the available expertise.

Airway Fluid/Lavage and Cellular Assessment

Currently, other than the assessment of airway specimens for microbiological purposes, the use of an airway cellular and inflammatory profile in children with chronic cough is currently limited to a supportive diagnosis and research rather than a definitive diagnosis. This is in contrast to that in adults with chronic cough in whom some have suggested the use of an airway inflammatory profile (*ie*, levels of primarily eosinophils) to direct therapy.[69,70]

Tests for Airway Hyperresponsiveness

Tests for airway hyperresponsiveness (AHR) are not used in routine practice in most pediatric pulmonary laboratories to diagnose asthma.[71] The presence of AHR does not mean that asthma is present in children,[72] and the demonstration of AHR in a child with isolated cough is unlikely to be helpful in predicting the later development of asthma[73] or the response to asthma medications.[74] Older studies[75–78] have stated that the presence of AHR in children with cough is said to be representative of asthma. However, these studies[75–78] were not placebo-controlled, and in them confounders were not adjusted for or unconventional definitions of AHR were used.

Spirometry

Spirometry is valuable in the diagnosis of reversible airway obstruction in children with chronic cough if an abnormality is present.[79,80] Spirometry can usually be reliably performed in children aged $>$ 6 years and in some children $>$ 3 years if trained pediatric personnel are present.[81]

Other Investigative Techniques

Airways resistance determined by the interrupter technique, which has not yet been established in clinical practice, may prove to be useful in detecting isolated cough associated with asthma.[82] Despite its application in research, there are still problems with intersubject variability and, hence, with the validity of its measurements when undertaken by different investigators.[83] To date, there have been no studies that have evaluated the role of nitric oxide (NO) or breath condensate in determining the etiology of chronic cough in children. There has been only one study[84] on bronchial biopsy in children with chronic cough. Heino and colleagues[84] described the association between ARI in children before the age of 1 year and epithelial inflammation in seven children with chronic cough ($>$ 3 months).[84]

Several studies[18,85,86] have described altered cough sensitivity (to capsaicin or acetic acid) in different disease processes. Increased cough sensitivity has been found in children with recurrent cough,[36] cough-dominant asthma,[86] and acute and postviral respiratory infections. However, tests for cough sensitivity are currently nondiagnostic, their sensitivity and specificity undefined, and their use still limited to research purposes.

Evaluation and Management of Children With Chronic Cough

For clinically practical reasons, we have divided cough into specific cough and nonspecific cough (Fig 1).[11] In specific cough, the etiology and necessity of further investigations is usually evident from the presence of coexisting symptoms and signs (Table 1). The presence of any of these symptoms suggests that the cough is likely indicative of an underlying disorder and that further complex investigations may be indicated. The type and depth of these investigations depend on clinical findings. Diagnoses that need to be considered include bronchiectasis, retained foreign body, aspiration lung disease, atypical respiratory infections, cardiac anomalies and interstitial lung disease, among others (see Fig 2, 3).

There are no published studies on the etiology of "dry cough" vs "moist/productive cough" in children. A moist cough putatively represents excess airway secretions.[17] Even in children with moist cough, though, a specific pediatric diagnostic category may not be found.[87] A chronic dry cough, on the other hand, may represent a dry phase of an otherwise usually moist cough.[17] Chronic cough in the absence of specific pointers (Table 1) in the medical history and physical examination is termed *nonspecific cough* (*ie*, cough is the only symptom). In nonspecific cough, the etiology is ill-defined; it has been speculated that the majority of cases are related to postviral cough and/or increased cough receptor sensitivity.[18,36] In the study by Callahan,[88] however, an

asthma-like condition was the most common diagnosis (the quality of cough was not specified in the study). After investigations are conducted (if necessary), some children may be found to have an underlying serious abnormality.[89] However, in the majority of children, nonspecific cough is most likely related to a nonserious etiology[23] or may spontaneously resolve, as evidenced in the placebo arms of RCTs[74,90,91] and cohort studies.[92–94] The remainder of this guideline discusses the available data on nonspecific cough. There is, though, an overlap among specific cough, nonspecific cough, and expected cough (Fig 1), and hence the need for a review of the case of any child with a chronic cough. Evidence-based management guidelines for cough associated with acute infections, as well as that associated with underlying respiratory and systemic disorders, are beyond the scope of this section, and disease-specific guidelines and/or evidence-based reviews for children are available for some diseases such as asthma,[6] community-acquired pneumonia,[3–5] bronchiolitis,[95] airway clearance methods,[96] and selective aspects of cystic fibrosis management,[97–99] in addition to that those provided by a United States-based resource (The National Guideline Clearinghouse [www.guideline.gov]). The list is far from exhaustive, and, although none of these guidelines are cough-specific, cough usually improves when the underlying disease is treated.

Recommendations

1. Children with chronic cough require careful and systematic evaluation for the presence of specific diagnostic indicators. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. Children with chronic cough should undergo, as a minimum, a chest radiograph and spirometry (if age appropriate). Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

3. In children with specific cough, further investigations may be warranted, except when asthma is the etiologic factor. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

4. Children with chronic productive purulent cough should always be investigated to document the presence or absence of bronchiectasis and to identify underlying and treatable causes such as cystic fibrosis and immune deficiency. Level of evidence, low; benefit, substantial; grade of recommendation, B

Asthma, Asthma-Like Conditions, and Cough in Children

Children with asthma may present with cough. However, the majority of children with isolated cough do not have asthma.[9,10,100] The use of isolated cough as a marker of asthma is indeed controversial with more recent evidence[11,100] showing that in most children, isolated cough does not represent asthma. Some hospital-based clinical studies[101,102] of children presenting with chronic cough have found asthma to be the most common cause, but others have not.[87,89] There is little doubt that the etiology of cough would depend on the setting, selection criteria of the children studied,[89,103] follow-up rate,[104] and depth of the clinical history, physical examination, and investigations performed. When airway profiles have been examined in children with isolated chronic cough, the studies[103,105,106] have shown very few children with airway inflammation that is consistent with asthma. Cough associated with asthma without a coexistent respiratory infection is usually dry.[6] This topic has been previously reviewed.[9] With space limitations, only an update of further studies (in addition to the studies on airway fluid assessment outlined in Table 2) is summarized in Table 3. A review[107] relating measurements of cough severity to those of asthma severity is also available. A further difficulty relating cough and asthma is the fact that cough is the most common symptom in patients presenting to doctors in the United States and Australia,[108,109] and viral respiratory infections, which also cause cough, are said to account for 80% of childhood asthma exacerbations.[110] It would be difficult to ascertain whether cough is secondary to asthma or to the respiratory viral infection.

Upper Airways Disorders and Cough in Children

In adults, upper airway cough syndrome (previously referred to as *postnasal drip syndrome*) has been reported[111,112] as a common cause of chronic cough. In children, although nasal discharge and cough have been reported as the two most prominent symptoms in children with chronic sinusitis (for 30 to 120 days),[113] the supportive evidence of cause and effect in children is less convincing.[114] Although sinusitis is commonly diagnosed in childhood, it can be rarely proven, and it is not associated with cough once atopy and doctor-diagnosed allergic rhinitis are controlled for.[115] The relationship between nasal secretions and cough is more likely linked by common etiology (infection and/or inflammation causing both) or is due to the clearing of secretions reaching the larynx. Abnormal sinus radiographs may be found in 18 to 82% of asymptomatic children.[116] A systematic review of acute sinusitis in children con-

cluded that "diagnostic modalities showed poor concordance, and treatment options were based on inadequate data."[117]

Turktas and colleagues[118] described increased extrathoracic AHR without bronchial AHR to methacholine in a group of children presenting with chronic cough, and other studies[119,120] have linked extrathoracic AHR to sinusitis and rhinitis in adults. Whether the presence of upper airway abnormalities causes or is the consequence of extrathoracic AHR is unknown. The repeatability and validity of extrathoracic AHR in children is also ill-defined. Therapeutic approaches in managing children with allergic rhinitis have been well-summarized by Fireman.[121] A single RCT[122] on adolescents and adults (n = 245) with allergic rhinitis using cough as an outcome measure showed that daytime cough difference between the active treatment arm (with mometasone furoate) and placebo was significant (p = 0.049). In comparison, a larger difference between groups was found for nasal symptoms, and there was no difference in nighttime cough.[122] There have been no RCTs on therapies for upper airway disorders in younger children with nonspecific cough.

GERD and Cough in Children

Several studies[123,124] have reported that esophageal disorders can trigger cough in children, and this occurs by several mechanisms. Whether the sensory pathway stimulation described in animal studies[125] also occurs in children is unknown. However, while GERD can be the reason for persistent cough,[124,126] cough can also provoke gastroesophageal reflux (GER) episodes in adults.[127,128] Data on cough itself causing GER described in adults is unavailable in children.[128] Proof that GERD causes chronic cough in children is rare,[123] and the relationship between the two is most likely complex.[129] As cough is very common in children and respiratory symptoms may exacerbate GER, it is difficult to differentiate cause and effect.[130] Infants often regurgitate,[131] yet few well infants cough with these episodes. The effects of fundoplication on cough and other respiratory symptoms are inconsistent.[132,133] There are a limited number of studies that have looked at the causes of chronic cough in children prospectively, but those that are available suggest that GERD is infrequently the sole cause of isolated cough in children. One prospective study[101] of the causes of chronic cough in children found only one child with GERD out of a series of 38. A more recent retrospective study[89] found coexistent GERD in 4 of 49 children with chronic cough. In contrast to data in adults whereby GERD is a frequent cause of chronic cough,[134,135] there is indeed little current convincing evidence that GERD is a common cause of isolated chronic cough in children.

Airway Lesions and Cough

Chronic cough has also been well-described in children with airway lesions.[136–139] Gormley and colleagues[139] described that 75% of children with congenital tracheomalacia secondary to congenital vascular anomaly had persistent cough at presentation. How commonly airway lesions are found in asymptomatic children is unknown, and how the symptom of cough relates to airway lesions can only be postulated. Airway malacia impedes the clearance of secretions,[138] and it is plausible that the prolonged duration of cough in these children relates to a bronchitic process distal to the lesion. Stradling[140] has described bronchomalacia secondary to chronic bronchitis in adults. However, which is the cause and which is the effect are unknown. Nevertheless, recurrent infections and pneumonia on the side of the airway lesion have been well-described,[138] and so has the misdiagnosis of asthma in children with airway malacia disorders.[138,141] The relationship between airway lesions and cough is not straightforward. Although persistent cough is listed as an indication for flexible bronchoscopy,[68,142] its role in this context has yet to be defined prospectively.

Environmental Pulmonary Toxicants

Exposure to environmental smoke increases the susceptibility to respiratory infections,[143,144] causes adverse respiratory health outcomes,[145] and increases coughing illnesses.[146,147] Increased environmental tobacco smoke (ETS) exposure has also been described in cohorts of children with chronic cough compared to children without cough.[103,148] However, the Tucson study[149] concluded that, "cough was not associated with parental smoking during the first decade of life," which contrasts with other epidemiologic and clinical studies[103,145,146,150] showing a close link between childhood cough and ETS exposure.

Exposure to indoor biomass combustion increases coughing illness associated with respiratory infections with an exposure-response effect.[151] Exposure to other ambient pollutants (*eg*, particulate matter,[152,153] nitrogen dioxide, and gas cooking[154]) is also associated with increased cough in children in both cross-sectional studies[152,153] and longitudinal studies,[155] especially in the presence of other respiratory illness such as asthma.[152] Some studies,[156,157] however, have not shown this effect, and this may be

related partially to problems in questionnaire-based epidemiologic studies on isolated and nocturnal cough.[9,27]

Nonasthmatic Eosinophilic Bronchitis and Allergy

Nonasthmatic eosinophilic bronchitis, which is a well-described cause of chronic cough in adults,[158] has not been recognized in children. "Allergic cough" is a poorly defined condition even in adults, and its relationship to childhood cough probably represents an overlap with asthma, nonasthmatic eosinophilic bronchitis, allergic rhinitis, and adenoid tonsillar hypertrophy.[159] The association between atopy and respiratory symptoms has been the subject of many epidemiologic studies.[160,161] Some have described[160,161] greater respiratory symptom chronicity,[162] while others have not. Inconsistent findings regarding cough and atopy are also present in the literature; reports of increased atopy (or diseases associated with atopy) in children with cough have been found in cohort and cross-sectional studies[163,164] as has as the absence of influence of atopy.[74,90,165,166] Cough as a functional symptom can also be mistaken for an allergic disorder in children.[167]

Chronic Nocturnal Cough

The major problem in utilizing the symptom of nocturnal cough is the unreliability and inconsistency of its reporting when compared to objective measurements.[56,57,168] This has been reviewed,[107,169] and hence only salient points and recent articles will be mentioned. Nocturnal cough is often used as a direct indicator of asthma as children with asthma are often reported to have troublesome nocturnal cough.[170] However, in the community-based study by Ninan and colleagues,[165] only a third of children with isolated nocturnal cough (*ie*, the absence of wheezing, shortness of breath, or chest tightness) had an asthma-like illness. To date, there have been no studies that have objectively documented that nocturnal cough is worse than daytime cough in children with unstable asthma. One study[171] has shown that cough frequency was higher during the day than at night in a group of children with stable asthma who were receiving treatment with inhaled corticosteroids (ICSs) yet had elevated levels of NO but not sputum eosinophils, which is arguably the best marker for eosinophilic inflammation in adults with stable asthma.[172] Whether the increased NO is a marker of asthma instability or is related to other causes of elevated NO levels (such as environmental pollutants)[173,174] is unknown. It is possible that nocturnal cough is considered to be more troublesome than daytime cough.

Respiratory Infections and Postinfections Cough

Recurrent URTIs and infections such as pertussis can cause chronic cough (Table 3). The natural history of cough associated with URTIs in children 0 to 4 years of age in the community has been summarized.[22] *Postviral cough* is a term that refers to the presence of cough after an acute viral respiratory infection. However, this has not been well-studied, and little is known about its pathophysiology or natural history beyond 25 days.[21] When a child who has not fully recovered from a URTI-related cough acquires a subsequent URTI, the coughing illness may seem prolonged. In the review by Monto,[40] the mean annual incidence of total respiratory illness per person-year ranges from 5 to 8 in children $<$ 4 years of age to 2.4 to 5.0 in children 10 to 14 years of age.[40]

Although pertussis, pertussis-like, and Mycoplasma infections classically cause cough that is associated with other symptoms, (*eg*, cough from pertussis infection is usually spasmodic,[175] and cough from Mycoplasma infection may be associated with other symptoms of a respiratory infection such as pharyngitis),[176] these infections can also cause persistent cough without other symptoms,[177] especially in the presence of process modifiers such as antibiotics and vaccination.[175] Pertussis should be suspected, especially if the child has had known contact with someone with a pertussis infection even if the child is fully immunized, as partial vaccine failure can occur.[178]

Medications and Treatment Side Effects

Chronic cough has been reported[179–181] as a side effect of the use of angiotensin-converting enzyme (ACE) inhibitors and of asthma medications immediately after inhalation,[182] and as a complication of chronic vagus nerve stimulation.[183] In one review,[181] chronic cough developed in only 1 of the 51 children (2%) who were treated with ACE inhibitors; yet, another study[180] reported cough in 7 of the 42 children (16.7%). In children, cough associated with ACE inhibitors resolves within days (*ie*, 3 to 7 days) after withdrawing the medication,[179,180] and may not recur when therapy with the medication is recommenced.[180]

Functional Respiratory Disorder (Psychogenic)

The many descriptions of cough with a functional or psychogenic overlay include the following: (1) habit cough, (2) tic cough, and (3) psychogenic cough. The distinctions between these categories may be unclear and possibly may reflect a spectrum of different severity.[62,184] This topic is covered in a

combined adult and pediatric section devoted to "habit cough and psychogenic cough."

Otogenic Causes: Arnold Ear-Cough Reflex

In approximately 2.3 to 4.2% of people, the auricular branch of the vagus nerve is present and the Arnold ear-cough reflex can be elicited (with bilateral occurrence in 0.3 to 2% of people).[185–187] The reflex can be elicited by palpation of the posteroinferior wall and rarely by palpation of the anteroinferior wall of the external acoustic meatus (ear canal).[185,187] Case reports[188–190] of chronic cough associated with ear canal stimulation from wax impaction, cholesteatoma, and acquired aberrant sensory referral post-cardiac transplant have been reported. In children, the significance of the ear reflex and cough was described as early as 1963,[191] although in 2002 it was reported again.[192] In our experience, this is a very rare cause of childhood chronic cough.

Inhalation of Foreign Body

Cough is the most common symptom in some series of foreign material inhalation but not in others.[193] In one series,[194] cough was present in 70% of patients, while other dominant symptoms included decreased breath sounds (53%) and wheezing (45%). A history of a choking episode was reported in 32% of patients, but when families were questioned in more detail the rate increased to 51%.[194] Presentations are usually acute,[195] but chronic cough can also be the presenting symptom in a previously missed foreign body inhalation.[196] A normal chest radiograph finding does not exclude foreign body inhalation, and a specific medical history should be sought because a missed foreign body can result in long-term pulmonary damage.[39]

Parental and Physician Expectations

Providing parents with information on the expected length of time until the resolution of ARIs may reduce their anxiety, and the need for medication use and additional consultation.[197] The appreciation of specific concerns and anxieties, and an understanding of why children present are thus important when caring for children with nonspecific cough. It has been argued[198] that quality of life is determined by expectations rather than by experience. Parental and professional expectations as well as the doctor's perceptions of patients' expectations influences consulting rates and the prescription of medications.[22,199,200] The use of cough medications and presentation to doctors were less likely in children with more highly educated mothers.[201] Mangione-Smith et al[202] described that "physicians' perceptions of parental expectations for antimicrobials was the only significant predictor of prescribing antimicrobials for conditions of presumed viral etiology and hellip." Earlier, Hutton et al[28] had showed that "parents who wanted medicine at the initial visit reported more improvement at follow-up, regardless of whether the child received drug, placebo, or no treatment." Physicians should be cognizant that "a parent navigating the Internet for information on the home management of cough in children will no doubt find incorrect advice among the search results."[203]

The concerns of parents presenting to general practitioners in the United States for their children's cough can be extreme and can include the following: fear of the child dying from choking; fear of asthma attack or cot death; and fear of permanent chest damage.[204] Other concerns that parents express are disturbed sleep and relief of discomfort.[204] Findings from a London specialist respiratory clinic were similar.[205] However, the burden of illness on children and their families has not been well-described.

Treatment of Nonspecific Cough

A summary of the treatment of nonspecific cough in children, the time to response, and the level of evidence is presented in Table 4. In the interest of space, only salient points will be discussed below, and readers are referred to the relevant studies for further information.

OTC Cough Medications

Systematic reviews have concluded that OTC cough medications have little, if any, benefit in the symptomatic control of acute cough in children,[12,16] and the American Academy of Pediatrics has advised[206] against the use of codeine and dextromethorphan for treating any type of cough. Moreover, the use of OTC cough remedies has been associated with significant morbidity and even with mortality.[207] OTC drugs are common unintentional ingestion medications in children < 5 years of age.[208] A Cochrane review[209] of symptomatic treatment of cough related to pertussis also found no significant benefit for therapy with diphenhydramine. A recent RCT[13] on two commonly used OTC cough medications and OTC medications containing antihistamine combinations are discussed below under the heading "Antihistamines." A review of these medications is available.[14]

Asthma Therapy

A systematic review[210] has shown that "there is no evidence to support using β_2-agonists in children

with acute cough and no evidence of airflow obstruction." There has been only one study[74] on the use of inhaled salbutamol in patients with chronic cough that also showed no benefit. There is also no evidence to support the use of anticholinergic agents[211] for the treatment of nonspecific cough in children. Nedocromil and cromoglycate reduce cough associated with asthma[212,213] and in children born prematurely.[214] A Cochrane review[215] has described an absence of data for its use. Old cohort studies have described the benefit of asthma therapy for that era (*ie*, oral orciprenaline, salbutamol syrup,[216,217] theophylline,[75,217] and metaproterenol with theophylline[79]) in abolishing cough.

Only two published RCTs[74,90] on ICSs for the treatment of chronic nonspecific cough in children exist, and both groups cautioned against the prolonged use of ICSs. There has been no RCT performed on the use of oral steroids for nonspecific cough in children. In cough associated with pertussis, dexamethasone provides no significant benefit for the symptomatic relief of cough.[209] Even in children with wheeze, an RCT[218] that was performed in 200 young children found that parent-initiated treatment with oral steroids conferred no benefit but was instead associated with a nonsignificant increase in hospitalizations ($p = 0.058$). Given that low-dose ICSs have been shown to be effective in the management of the majority of cases of childhood asthma,[219–221] and the reported significant adverse events occurring with high-dose ICSs,[222,223] we suggest the use of a 400 μg/d equivalent dose of budesonide (or beclomethasone) if a trial of asthma therapy is warranted. As the earlier studies[75,79,80,224] in adults and children that utilized medications for asthma for the era (*eg*, nonsteroidal agents such as theophylline[75] and major tranquilizers[224]) reported that cough related to asthma completely resolved after 2 to 7 days, we recommend reassessment after 2 to 3 weeks. Cough that is unresponsive to treatment with ICSs should not be treated with increased doses of ICSs. If the cough resolved with ICS use, clinicians should still be cognizant that the child does not necessarily have asthma, and the child should be reevaluated after asthma treatment has been stopped. The resolution of cough may occur with the period effect (*ie*, spontaneous resolution)[59] or a transient response.

Antimicrobials

There have been two randomized studies[225,226] that have examined the use of antimicrobial agents. Although the entry criterion was cough lasting for > 10 days, 23% of children had cough of > 30 days duration, and the mean duration of cough in the study by Gottfarb and Brauner[225] was 3 to 4 weeks. In both studies, nasopharyngeal colonization showed a predominance of *Moraxella catarrhalis*, and a significant improvement was seen in the antimicrobial treatment arm. In children with persistent nasal discharge or in older children with radiographically confirmed sinusitis, a Cochrane review[227] showed that a 10-day course of antimicrobial agents reduces the probability of the persistence of cough in the short to medium term. However, the "number needed to treat" was relatively high at eight patients.[227] In another systematic review[117] of uncomplicated sinusitis in children, the clinical improvement rate in RCTs was 88% with antimicrobial therapy and 60% with no antimicrobial therapy. The guidelines of the American Academy of Family Physicians[228] have suggested the restriction of antimicrobial use to those persons with acute sinusitis symptoms and cough that does not improve after 10 days. In a Cochrane review,[229] the use of antimicrobial agents confers no benefit in patients with acute cough associated with common colds.

Antihistamines

In contrast to the data in adults, the efficacy of antihistamine agents in relieving cough in children is minimal, if any. For acute cough, a systematic review[12] of antihistamine and nasal decongestion combinations and antihistamines in OTC medications has shown that these pharmaceuticals were no more likely than placebo to reduce acute cough in children. There have been, however, no studies on chronic cough. A recent RCT[13] also showed that diphenhydramine and dextromethorphan were no different than placebo in reducing nocturnal cough or sleep disturbance in both the children and parents. Like other RCTs, there was a significant improvement in both the placebo and active arms for the four cough-related outcomes measured.[13] In a metaanalysis[230] of antihistamine treatment for the common cold (in contrast to cough as an outcome measure), neither antihistamine monotherapy nor combinations of antihistamines with decongestants were effective in children (participants were ≤ 15 years of age) in reducing symptoms. However, in older children (one study included children > 12 years of age, but participants in the rest of studies were > 18 years of age) and in adults, "most trials show some beneficial effect on general recovery as well as on nasal symptoms."[230]

GERD Therapies

A clinical practice guideline[31] on the evaluation and management of children with GERD is available. There are no data on the time for resolution of

cough related to GERD in children, and no RCT has been conducted on the use of proton pump inhibitors for the treatment of cough in children. A Cochrane review[26] on GERD therapies (milk thickening[231,232] and cisapride or domperidone[233]) for cough has failed to find a beneficial effect. A therapeutic trial of high-dose proton pump inhibitors, arguably the best medication for acid-GERD associated cough in adults,[234–236] requires research in children. In a Cochrane review[237] on metoclopramide, thickened feedings, and positioning for GER in children < 2 years of age, the effect of metoclopramide on GER was not significant between treatment and placebo groups, and cough was not an outcome in these studies. Although case series have shown the link between supraesophageal symptoms and GER in children, there is a lack of convincing data, summarized as follows by Rudolph[238]: "No studies have definitively demonstrated symptom improvement with medical or surgical therapy for the latter symptom presentations." In the American guidelines for pediatric GER,[31] the section on upper airway symptoms included a discussion on cough and GER. It concluded that ". . . there is insufficient evidence and experience in children for a uniform approach to diagnosis and treatment."[31] While there has been a sporadic case report suggesting that cough can occur as an adverse event in reaction to therapy with omeprazole in adults,[239] there have been no pediatric reports.

Cessation of Exposure to ETS and Other Environmental Toxicants

In the management of cough in any child, irrespective of the etiology, attention to exacerbating factors is encouraged. The American Academy of Pediatrics has a policy statement on tobacco exposure in pediatrics.[240] There have been no RCTs that have examined the effect of the cessation of ETS or other toxic environmental exposure on cough in children. A single report[241] was found on the cessation of parental smoking as a successful form of therapy for cough in children. Behavioral counseling for mothers who smoke has been shown to reduce the ETS exposure of young children in both reported and objective measures of ETS.[242] However, the effect of ETS reduction on children's symptoms was not studied.[242] In one uncontrolled study,[243] house heating had the greatest impact on reducing nocturnal cough in children with asthma.

Physician and Parental Expectations

Educational input is most successful when it addresses the child's specific condition. Exploring and understanding the specific concerns of parents is initially required. Written information without discussion provides only modest benefit in changing perceptions and behavior.[244] In an RCT, Little et al[245] sent booklets and sheets that included information on minor respiratory tract infections and found that, while patients felt more confident managing their minor illness, the effect on subsequent attendance with a minor illness was only modest. Taylor et al[246] conducted an RCT examining the effect of a pamphlet and a videotape promoting the judicious use of antibiotics and found that their simple educational effort was successful in modifying parental attitudes about antibiotics and concluded "information about specific childhood conditions may be more effective in changing attitudes than more general information about antibiotic usage."[246]

Recommendations

5. In children with chronic cough, the etiology should be defined and treatment should be etiologically based. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

6. In children with nonspecific cough, cough may spontaneously resolve, but children should be reevaluated for the emergence of specific etiologic pointers (see Table 1). Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In children with nonspecific cough and risk factors for asthma, a short trial (*ie*, 2 to 4 weeks) of beclomethasone, 400 μg/d, or the equivalent dosage with budesonide may be warranted. However, most children with nonspecific cough do not have asthma. In any case, these children should always be reevaluated in 2 to 4 weeks. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

8. In children who have started therapy with a medication, if the cough does not resolve during the medication trial within the expected response time, the medication should be withdrawn and other diagnoses considered. Level of evidence, low; benefit, intermediate; grade of recommendation, C

9. In children with cough, cough suppressants and other OTC cough medicines should not be used as patients, especially young children, may experience significant morbidity and mortality. Level of evidence, good; benefit, none; grade of recommendation, D

10. In children with nonspecific cough, parental expectations should be determined, and the specific concerns of the parents should be

sought and addressed. Level of evidence, low; benefit, intermediate; grade of recommendation, E/B

11. In all children with cough, exacerbating factors such as ETS exposure should be determined and interventional options for the cessation of exposure advised or initiated. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. Children should be managed according to the studies and guidelines for children (when available), because etiologic factors and treatments in children are sometimes different from those in adults. Level of evidence, low; benefit, substantial; grade of recommendation, B

13. In children ≤ 14 years of age with chronic cough, when pediatric-specific cough recommendations are unavailable, adult recommendations should be used with caution. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

Conclusion

Children with cough should be managed according to child-specific guidelines, which differ from those for adults as the etiologic factors and treatments in children are sometimes different from those in adults. In children, cough is very common and, in the majority of children, is reflective of expected childhood respiratory infections. However, cough may also be representative of a significant serious disorder, and all children with chronic cough should have a thorough clinical review to identify pointers that are suggestive of an underlying respiratory and/or systemic illness.

Cough in children should be treated based on etiology, and there is little evidence for using medications for the symptomatic relief of cough. If medications are used, it is imperative that the children are followed up and therapy with those medications stopped if there is no effect on the cough within an expected time frame. Evaluation of the time to response is important. Irrespective of diagnosis, environmental influences and parental expectations should be discussed and managed accordingly. Cough often impacts the quality of life of both children and parents, and the exploration of parental expectations and fears is often valuable in the management of cough in children.

Summary of Recommendations

1. Children with chronic cough require careful and systematic evaluation for the presence of specific diagnostic indicators. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. Children with chronic cough should undergo, as a minimum, a chest radiograph and spirometry (if age appropriate). Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

3. In children with specific cough, further investigations may be warranted, except when asthma is the etiologic factor. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

4. Children with chronic productive purulent cough should always be investigated to document the presence or absence of bronchiectasis and to identify underlying and treatable causes such as cystic fibrosis and immune deficiency. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In children with chronic cough, the etiology should be defined and treatment should be etiologically based. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

6. In children with nonspecific cough, cough may spontaneously resolve, but children should be reevaluated for the emergence of specific etiologic pointers (see Table 1). Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In children with nonspecific cough and risk factors for asthma, a short trial (*ie*, 2 to 4 weeks) of beclomethasone, 400 μg/d, or the equivalent dosage with budesonide may be warranted. However, most children with nonspecific cough do not have asthma. In any case, these children should always be reevaluated in 2 to 4 weeks. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

8. In children who have started therapy with a medication, if the cough does not resolve during the medication trial within the expected response time, the medication should be withdrawn and other diagnoses considered. Level of evidence, low; benefit, intermediate; grade of recommendation, C

9. In children with cough, cough suppressants and other OTC cough medicines should not be used as patients, especially young children, may experience significant morbidity and mortality. Level of evidence, good; benefit, none;

grade of recommendation, D

10. In children with nonspecific cough, parental expectations should be determined, and the specific concerns of the parents should be sought and addressed. Level of evidence, low; benefit, intermediate; grade of recommendation, E/B

11. In all children with cough, exacerbating factors such as ETS exposure should be determined and interventional options for the cessation of exposure advised or initiated. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. Children should be managed according to the studies and guidelines for children (when available), because etiologic factors and treatments in children are sometimes different from those in adults. Level of evidence, low; benefit, substantial; grade of recommendation, B

13. In children ≤ 14 years of age with chronic cough, when pediatric-specific cough recommendations are unavailable, adult recommendations should be used with caution. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

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References

1 Smyth RL. Research with children. BMJ 2001; 322:1377–1378
2 Sinaiko AR, Daniels SR. The use of short-acting nefedipine in children with hypertension: another example of the need for comprehensive drug testing in children. J Pediatr 2001; 139:7–9
3 British Thoracic Society. BTS guidelines for the management of community acquired pneumonia in childhood. Thorax 2002; 57(suppl):I1–I24
4 Jadavji T, Law B, Lebel MH, et al. A practical guide for the diagnosis and treatment of pediatric pneumonia. Can Med Assoc J 1997; 156:S703–S711
5 Nelson JD. Community-acquired pneumonia in children: guidelines for treatment. Pediatr Infect Dis J 2000; 19:251–253
6 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax 2003; 58(suppl):i1–i94
7 Chernick V, Boat TF. Kendig's disorders of the respiratory tract in children. Philadelphia, PA: WB Saunders, 1998
8 Taussig LM, Landau LI. Pediatric respiratory medicine. St. Louis, MO: Mosby, 1999
9 Chang AB. State of the art: cough, cough receptors, and asthma in children. Pediatr Pulmonol 1999; 28:59–70
10 McKenzie S. Cough: but is it asthma? Arch Dis Child 1994; 70:1–2
11 Chang AB, Asher MI. A review of cough in children. J Asthma 2001; 38:299–309
12 Schroeder K, Fahey T. Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials. Arch Dis Child 2002; 86:170–175
13 Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics 2004; 114:e85–e90
14 Kelly LF. Pediatric cough and cold preparations. Pediatr Rev 2004; 25:115–123
15 Hestand HE, Teske DW. Diphenhydramine hydrochloride intoxication. J Pediatr 1977; 90:1017–1018
16 Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev (database online). Issue 4; 2004
17 Chang AB, Eastburn MM, Gaffney J, et al. Cough quality in children: a comparison of subjective vs. bronchoscopic findings. Respir Res 2005; 6:3
18 Chang AB, Phelan PD, Sawyer SM, et al. Airway hyperresponsiveness and cough-receptor sensitivity in children with recurrent cough. Am J Respir Crit Care Med 1997; 155: 1935–1939
19 Chang AB, Masel JP, Boyce NC, et al. Non-CF bronchiectasis-clinical and HRCT evaluation. Pediatr Pulmonol 2003; 35:477–483
20 Chang AB. Defining the cough spectrum and reviewing the evidence for treating non-specific cough in children. Curr Pediatr Rev 2005; 1:283–296
21 Hay AD, Wilson A, Fahey T, et al. The duration of acute cough in pre-school children presenting to primary care: a prospective cohort study. Fam Pract 2003; 20:696–705
22 Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. Br J Gen Pract 2002; 52:401–409
23 Bush A. Paediatric problems of cough. Pulm Pharmacol Ther 2002; 15:309–315
24 de Benedictis FM, Selvaggio D, de Benedictis D. Cough, wheezing and asthma in children: lesson from the past. Pediatr Allergy Immunol 2004; 15:386–393
25 Wubbel C, Faro A. Chronic cough in children. Pediatr Case Rev 2003; 3:95–104
26 Chang AB, Gaffney J, Connor FC, et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev (database online). Issue 2; 2005
27 Dales RE, White J, Bhumgara C, et al. Parental reporting of children's' coughing is biased. Eur J Epidemiol 1997; 13: 541–545
28 Hutton N, Wilson MH, Mellits ED, et al. Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. J Pediatr 1991; 118:125–130
29 Bachrach LK. Bare-bones fact: children are not small adults. N Engl J Med 2004; 351:924–926
30 Couriel J. Infection in children. In: Ellis M, ed. Infectious diseases of the respiratory tract. Cambridge, UK: Cambridge University Press, 1998: 406–429
31 Rudolph CD, Mazur LJ, Liptak GS, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001; 32(suppl):S1–S31

32 Nunn JF. Applied respiratory physiology. London, UK: Butterworths, 1993
33 Polgar G, Weng T. The functional development of the respiratory system from the period of gestation to adulthood. Am Rev Respir Dis 1979; 120:625–695
34 Thach BT. Maturation and transformation of reflexes that protect the laryngeal airway from liquid aspiration from fetal to adult life. Am J Med 2001; 111(suppl):69S–77S
35 Kastelik JA, Thompson RH, Aziz I, et al. Sex-related differences in cough reflex sensitivity in patients with chronic cough. Am J Respir Crit Care Med 2002; 166:961–964
36 Chang AB, Phelan PD, Sawyer SM, et al. Cough sensitivity in children with asthma, recurrent cough, and cystic fibrosis. Arch Dis Child 1997; 77:331–334
37 Undem BJ, Carr MJ, Kollarik M. Physiology and plasticity of putative cough fibres in the Guinea pig. Pulm Pharmacol Ther 2002; 15:193–198
38 Joad JP, Munch PA, Bric JM, et al. Passive smoke effects on cough and airways in young guinea pigs: role of brainstem substance P. Am J Respir Crit Care Med 2004; 169:499–504
39 Karakoc F, Karadag B, Akbenlioglu C, et al. Foreign body aspiration: what is the outcome? Pediatr Pulmonol 2002; 34:30–36
40 Monto AS. Studies of the community and family: acute respiratory illness and infection. Epidemiol Rev 1994; 16: 351–373
41 Leder K, Sinclair MI, Mitakakis TZ, et al. A community-based study of respiratory episodes in Melbourne, Australia. Aust N Z J Public Health 2003; 27:399–404
42 Brenner DJ. Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. Pediatr Radiol 2002; 32:228–233
43 Taussig LM, Smith SM, Blumenfeld R. Chronic bronchitis in childhood: what is it? Pediatrics 1981; 67:1–5
44 Nwanyanwu O, Nyangulu D, Salaniponi F. Persistent cough in patients using an urban chest clinic in Malawi. Trop Doct 1996; 26:165–167
45 Singleton R, Morris A, Redding G, et al. Bronchiectasis in Alaska Native children: causes and clinical courses. Pediatr Pulmonol 2000; 29:182–187
46 Irwin RS, Curley FJ, French CL. Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 1990; 141:640–647
47 Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. Chest 1998; 114:133S–181S
48 Phelan PD, Asher MI. Recurrent and persistent cough in children. N Ethicals J 1999; June:41–45
49 Hsu JY, Stone RA, Logan-Sinclair RB, et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J 1994; 7:1246–1253
50 O'Connor GT, Weiss ST. Clinical and symptom measures. Am J Respir Crit Care Med 1994; 149:S21–S28
51 de Blic J, Thomson A. Short-term clinical measurement: acute severe episodes. Eur Respir J Suppl 1996; 21:4s–7s
52 Munyard P, Bush A. How much coughing is normal? Arch Dis Child 1996; 74:531–534
53 Chang AB, Phelan PD, Robertson CF, et al. Frequency and perception of cough severity. J Paediatr Child Health 2001; 37:142–145
54 Bonaccorso SN, Sturchio JL. For and against: direct to consumer advertising is medicalising normal human experience; against. BMJ 2002; 324:910–911
55 Brunekreef B, Groot B, Rijcken B, et al. Reproducibility of childhood respiratory symptom questions. Eur Respir J 1992; 5:930–935
56 Archer LNJ, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child 1985; 60:473–474
57 Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol 1993; 15:209–211
58 Clifford RD, Radford M, Howell JB, et al. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma. Arch Dis Child 1989; 64:1118–1125
59 Evald T, Munch EP, Kok-Jensen A. Chronic non-asthmatic cough is not affected by inhaled beclomethasone dipropionate: a controlled double blind clinical trial. Allergy 1989; 44:510–514
60 Eccles R. The powerful placebo in cough studies? Pulm Pharmacol Ther 2002; 15:303–308
61 Rietveld S, Van Beest I, Everaerd W. Psychological confounds in medical research: the example of excessive cough in asthma. Behav Res Ther 2000; 38:791–800
62 Butani L, O'Connell EJ. Functional respiratory disorders. Ann Allergy Asthma Immunol 1997; 79:91–99
63 Rietveld S, Rijssenbeek-Nouwens LH, Prins PJ. Cough as the ambiguous indicator of airway obstruction in asthma. J Asthma 1999; 36:177–186
64 Osika E, Muller MH, Boccon-Gibod L, et al. Idiopathic pulmonary fibrosis in infants. Pediatr Pulmonol 1997; 23: 49–54
65 Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 1996; 156:997–1003
66 Tiddens HA. Detecting early structural lung damage in cystic fibrosis. Pediatr Pulmonol 2002; 34:228–231
67 Webb WR, Muller NL, Naidich DP. Airway diseases: high-resolution CT of the lung. Philadelphia, PA: Lippincott, Williams & Wilkins, 2001; 467–546
68 de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. Eur Respir J 2002; 20:1271–1276
69 Pizzichini MM, Pizzichini E, Parameswaran K, et al. Non-asthmatic chronic cough: no effect of treatment with an inhaled corticosteroid in patients without sputum eosinophilia. Can Respir J 1999; 6:323–330
70 Hargreave FE, Leigh R. Induced sputum, eosinophilic bronchitis, and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 160:S53–S57
71 Wilson N, Silverman M. Bronchial responsiveness and its measurement. In: Silverman M, ed. Childhood asthma and other wheezing disorders. London, UK: Chapman & Hall, 1995; 142–174
72 Pin I, Radford S, Kolendowicz R, et al. Airway inflammation in symptomatic and asymptomatic children with methacholine hyperresponsiveness. Eur Respir J 1993; 6:1249–1256
73 Galvez RA, McLaughlin FJ, Levison H. The role of the methacholine challenge in children with chronic cough. J Allergy Clin Immunol 1987; 79:331–335
74 Chang AB, Phelan PD, Carlin J, et al. Randomised controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Arch Dis Child 1998; 79:6–11
75 Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperreactivity. Pediatrics 1981; 67:6–12
76 Paganin F, Seneterre E, Chanez P, et al. Computed tomography of the lungs in asthma: influence of disease severity and etiology. Am J Respir Crit Care Med 1996; 153:110–114
77 de Benedictis FM, Canny GJ, Levison H. Methacholine inhalational challenge in the evaluation of chronic cough in

children. J Asthma 1986; 23:303–308
78 Nishimura H, Mochizuki H, Tokuyama K, et al. Relationship between bronchial hyperresponsiveness and development of asthma in children with chronic cough. Pediatr Pulmonol 2001; 31:412–418
79 Konig P. Hidden asthma in children. Am J Dis Child 1981; 135:1053–1055
80 Hannaway PJ, Hopper GDK. Cough variant asthma in children. JAMA 1982; 247:206–208
81 Zapletal A, Chalupova J. Forced expiratory parameters in healthy preschool children (3–6 years of age). Pediatr Pulmonol 2003; 35:200–207
82 McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. Eur Respir J 2000; 15:833–838
83 Klug B, Nielsen KG, Bisgaard H. Observer variability of lung function measurements in 2–6-yr-old children. Eur Respir J 2000; 16:472–475
84 Heino M, Juntunen-Backman K, Leijala M, et al. Bronchial epithelial inflammation in children with chronic cough after early lower respiratory tract illness. Am Rev Respir Dis 1990; 141:428–432
85 Shimizu T, Mochizuki H, Morikawa A. Effect of influenza A virus infection on acid-induced cough response in children with asthma. Eur Respir J 1997; 10:71–74
86 Chang AB, Phelan PD, Robertson CF. Cough receptor sensitivity in children with acute and non-acute asthma. Thorax 1997; 52:770–774
87 Seear M, Wensley D. Chronic cough and wheeze in children: do they all have asthma? Eur Respir J 1997; 10:342–345
88 Callahan CW. Etiology of chronic cough in a population of children referred to a pediatric pulmonologist. J Am Board Fam Pract 1996; 9:324–327
89 Thomson F, Masters IB, Chang AB. Persistent cough in children: overuse of medications. J Paediatr Child Health 2002; 38:578–581
90 Davies MJ, Fuller P, Picciotto A, et al. Persistent nocturnal cough: randomised controlled trial of high dose inhaled corticosteroid. Arch Dis Child 1999; 81:38–44
91 Bernard DW, Goepp JG, Duggan AK, et al. Is oral albuterol effective for acute cough in non-asthmatic children? Acta Paediatr 1999; 88:465–467
92 Brooke AM, Lambert PC, Burton PR, et al. The natural history of respiratory symptoms in preschool children. Am J Respir Crit Care Med 1995; 52:1872–1878
93 Brooke AM, Lambert PC, Burton PR, et al. Recurrent cough: natural history and significance in infancy and early childhood. Pediatr Pulmonol 1998; 26:256–261
94 Zimmerman B, Silverman FS, Tarlo SM, et al. Induced sputum: comparison of postinfectious cough with allergic asthma in children. J Allergy Clin Immunol 2000; 105:495–499
95 Panitch HB. Respiratory syncytial bronchiolitis: supportive care and therapies designed to overcome airway obstruction. Pediatr Infect Dis J 2003; 22:S83–S38
96 Wallis C, Prasad A. Who needs chest physiotherapy? Moving from anecdote to evidence. Arch Dis Child 1999; 80:393–397
97 Baumer JH. Evidence based guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. Arch Dis Child 2003; 88:1126–1127
98 Jackson A. Clinical guidelines for cystic fibrosis care: summary of guidelines prepared by a working group of the Cystic Fibrosis Trust, the British Paediatric Association and the British Thoracic Society. J R Coll Physicians Lond 1996; 30:305–308
99 Doring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. Eur Respir J 2000; 16:749–767
100 Henry RL. All that coughs is not asthma [editorial]. Pediatr Pulmonol 1999; 28:1–2
101 Holinger LD. Chronic cough in infants and children. Laryngoscope 1986; 96:316–322
102 Callahan CW. Cough with asthma: variant or norm? J Pediatr 1996; 128:440
103 Gibson PG, Simpson JL, Chalmers AC, et al. Airway eosinophilia is associated with wheeze but is uncommon in children with persistent cough and frequent chest colds. Am J Respir Crit Care Med 2001; 164:977–981
104 Faniran AO, Peat JK, Woolcock AJ. Persistent cough: is it asthma? Arch Dis Child 1998; 79:411–414
105 Fitch PS, Brown V, Schock BC, et al. Chronic cough in children: bronchoalveolar lavage findings. Eur Respir J 2000; 16:1109–1114
106 Marguet C, Jouen Boedes F, Dean TP, et al. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. Am J Respir Crit Care Med 1999; 159:1533–1540
107 Chang AB. Monitoring cough: diary, electronic monitoring and significance in asthma. In: Gibson PG, ed. Monitoring asthma: lung biology in health and disease. London, UK: Marcel Dekker, 2006 (in press)
108 Britt H, Miller GC, Knox S, et al. Bettering the evaluation and care of health: a study of general practice activity. Canberra, ACT, Australia: Australian Institute of Health and Welfare, 2002
109 Cherry DK, Burt CW, Woodwell DA. National ambulatory medical care survey: 2001 summary. Adv Data 2003; 337:1–44
110 Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 1995; 310:1225–1229
111 Irwin RS, Pratter MR, Holland PS, et al. Postnasal drip causes cough and is associated with reversible upper airway obstruction. Chest 1984; 85:346–352
112 Curley FJ, Irwin RS, Pratter MR, et al. Cough and the common cold. Am Rev Respir Dis 1988; 138:305–311
113 Wald ER, Byers C, Guerra N, et al. Subacute sinusitis in children. J Pediatr 1989; 115:28–32
114 Campanella SG, Asher MI. Current controversies: sinus disease and the lower airways. Pediatr Pulmonol 2001; 31:165–172
115 Lombardi E, Stein RT, Wright AL, et al. The relation between physician-diagnosed sinusitis, asthma, and skin test reactivity to allergens in 8-year-old children. Pediatr Pulmonol 1996; 22:141–146
116 Shopfner CE, Rossi JO. Roentgen evaluation of the paranasal sinuses in children. AJR Am J Roentgenol 1973; 118:176–186
117 Ioannidis JP, Lau J. Technical report: evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: a systematic overview. Pediatrics 2001; 108:E57
118 Turktas I, Dalgic N, Bostanci I, et al. Extrathoracic airway responsiveness in children with asthma-like symptoms, including chronic persistent cough. Pediatr Pulmonol 2002; 34:172–180
119 Bucca C, Rolla G, Brussino L, et al. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? Lancet 1995; 346:791–795
120 Rolla G, Colagrande P, Scappaticci E, et al. Damage of the pharyngeal mucosa and hyperresponsiveness of airway in sinusitis. J Allergy Clin Immunol 1997; 100:52–57
121 Fireman P. Therapeutic approaches to allergic rhinitis:

treating the child. J Allergy Clin Immunol 2000; 105:S616–S621
122 Gawchik S, Goldstein S, Prenner B, et al. Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. Ann Allergy Asthma Immunol 2003; 90:416–421
123 Yellon RF, Coticchia J, Dixit S. Esophageal biopsy for the diagnosis of gastroesophageal reflux-associated otolaryngologic problems in children. Am J Med 2000; 108(suppl): 131S–138S
124 Cucchiara S, Santamaria F, Minella R, et al. Simultaneous prolonged recordings of proximal and distal intraesophageal pH in children with gastroesophageal reflux disease and respiratory symptoms. Am J Gastroenterol 1995; 90:1791–1796
125 Daoui S, Agostino B, Gallelli L, et al. Tachykinins and airway microvascular leakage induced by HCl intra-oesophageal instillation. Eur Respir J 2002; 20:268–273
126 Orenstein SR, Orenstein DM. Gastroesophageal reflux and respiratory disease in children. J Pediatr 1988; 112:847–858
127 Gastal OL, Castell JA, Castell DO. Frequency and site of gastroesophageal reflux in patients with chest symptoms: studies using proximal and distal pH monitoring. Chest 1994; 106:1793–1796
128 Laukka MA, Cameron AJ, Schei AJ. Gastroesophageal reflux and chronic cough: which comes first? J Clin Gastroenterol 1994; 19:100–104
129 Johnston BT, Gideon RM, Castell DO. Excluding gastroesophageal reflux disease as the cause of chronic cough [editorial]. J Clin Gastroenterol 1996; 22:168–169
130 Gilger MA. Pediatric otolaryngologic manifestations of gastroesophageal reflux disease. Curr Gastroenterol Rep 2003; 5:247–252
131 Treem WR, Davis PM, Hyams JS. Gastroesophageal reflux in the older child: presentation, response to treatment and long-term follow up. Clin Pediatr (Phila) 1991; 30:435–440
132 Tashjian DB, Tirabassi MV, Moriarty KP, et al. Laparoscopic Nissen fundoplication for reactive airway disease. J Pediatr Surg 2002; 37:1021–1023
133 Norrashidah AW, Henry RL. Fundoplication in children with gastro-oesophageal reflux disease. J Paediatr Child Health 2002; 38:156–159
134 Irwin RS, Madison JM. The persistently troublesome cough. Am J Respir Crit Care Med 2002; 165:1469–1474
135 Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 1981; 123:413–417
136 Masters IB, Chang AB, Patterson L, et al. Series of laryngomalacia, tracheomalacia, and bronchomalacia disorders and their associations with other conditions in children. Pediatr Pulmonol 2002; 34:189–195
137 Wood RE. Localised tracheomalacia or bronchomalacia in children with intractable cough. J Pediatr 1997; 116:404–406
138 Finder JD. Primary bronchomalacia in infants and children. J Pediatr 1997; 130:59–66
139 Gormley PK, Colreavy MP, Patil N, et al. Congenital vascular anomalies and persistent respiratory symptoms in children. Int J Pediatr Otorhinolaryngol 1999; 51:23–31
140 Stradling P. Diagnostic bronchoscopy. London, UK: Longman Group, 1991; 1–185
141 Bush A. Left bronchial isomerism, normal atrial arrangement and bronchomalacia mimicking asthma: a new syndrome? Eur Respir J 1999; 14:475–477
142 Nussbaum E. Pediatric fiberoptic bronchoscopy: clinical experience with 2,836 bronchoscopies. Pediatr Crit Care Med 2002; 3:171–176
143 Cohen S, Tyrrell DA, Russell MA, et al. Smoking, alcohol consumption, and susceptibility to the common cold. Am J Public Health 1993; 83:1277–1283
144 Wu-Williams AH, Samet JM. Environmental tobacco smoke: exposure-response relationships in epidemiologic studies. Risk Anal 1990; 10:39–48
145 Li JS, Peat JK, Xuan W, et al. Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. Pediatr Pulmonol 1999; 27: 5–13
146 Couriel JM. Passive smoking and the health of children. Thorax 1994; 49:731–734
147 Lister SM, Jorm LR. Parental smoking and respiratory illnesses in Australian children aged 0–4 years: ABS 1989–90 National Health Survey results. Aust N Z J Public Health 1998; 22:781–786
148 Chang AB, Harrhy VA, Simpson JL, et al. Cough, airway inflammation and mild asthma exacerbation. Arch Dis Child 2002; 86:270–275
149 Stein RT, Holberg CJ, Sherrill D, et al. Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. Am J Epidemiol 1999; 149:1030–1037
150 Charlton A. Children's coughs related to parental smoking. BMJ 1984; 288:1647–1649
151 Ezzati M, Kammen D. Indoor air pollution from biomass combustion and acute respiratory infections in Kenya: an exposure-response study. Lancet 2001; 358:619–624
152 Vedal S, Petkau J, White R, et al. Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. Am J Respir Crit Care Med 1998; 157:1034–1043
153 Hirsch T, Weiland SK, von Mutius E, et al. Inner city air pollution and respiratory health and atopy in children. Eur Respir J 1999; 14:669–677
154 Holscher B, Heinrich J, Jacob B, et al. Gas cooking, respiratory health and white blood cell counts in children. Int J Hyg Environ Health 2000; 203:29–37
155 Dodge R, Solomon P, Moyers J, et al. A longitudinal study of children exposed to sulfur oxides. Am J Epidemiol 1985; 121:720–736
156 Salameh PR, Baldi I, Brochard P, et al. Respiratory symptoms in children and exposure to pesticides. Eur Respir J 2003; 22:507–512
157 Roemer W, Clench-Aas J, Englert N, et al. Inhomogeneity in response to air pollution in European children (PEACE project). Occup Environ Med 1999; 56:86–92
158 Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. Thorax 2002; 57:178–182
159 Lack G. Pediatric allergic rhinitis and comorbid disorders. J Allergy Clin Immunol 2001; 108:S9–S15
160 Mertsola J, Ziegler T, Ruuskanen O, et al. Recurrent wheezy bronchitis and viral respiratory infections. Arch Dis Child 1991; 66:124–129
161 Clough JB, Holgate ST. Episodes of respiratory morbidity in children with cough and wheeze. Am J Respir Crit Care Med 1994; 150:48–53
162 Clough JB, Williams JD, Holgate ST. Effect of atopy on the natural history of symptoms, peak expiratory flow, and bronchial responsiveness in 7- and 8-year-old children with cough and wheeze. Am Rev Respir Dis 1991; 143:755–760
163 Powell CVE, Primhak RA. Stability of respiratory symptoms in unlabelled wheezy illness and nocturnal cough. Arch Dis Child 1996; 75:385–391

164 Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperesponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. J Allergy Clin Immunol 1990; 85:65–74
165 Ninan TK, Macdonald L, Russel G. Persistent nocturnal cough in childhood: a population based study. Arch Dis Child 1995; 73:403–407
166 Wright AL, Holberg CJ, Morgan WJ, et al. Recurrent cough in childhood and its relation to asthma. Am J Respir Crit Care Med 1996; 153:1259–1265
167 Niggemann B. Functional symptoms confused with allergic disorders in children and adolescents. Pediatr Allergy Immunol 2002; 13:312–318
168 Chang AB, Newman RG, Carlin J, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J 1998; 11:462–466
169 Chang AB. Cough as a marker of asthma control in children. In: Tersa M, ed. Focus on asthma research. New York, NY: Nova Medical Books, 2005: 289–305
170 Meijer GG, Postma DS, Wempe JB, et al. Frequency of nocturnal symptoms in asthmatic children attending a hospital out-patient clinic. Eur Respir J 1995; 8:2076–2080
171 Li AM, Lex C, Zacharasiewicz A, et al. Cough frequency in children with stable asthma: correlation with lung function, exhaled nitric oxide, and sputum eosinophil count. Thorax 2003; 58:974–978
172 Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002; 360:1715–1721
173 Sundblad BM, Larsson BM, Palmberg L, et al. Exhaled nitric oxide and bronchial responsiveness in healthy subjects exposed to organic dust. Eur Respir J 2002; 20:426–431
174 Franklin P, Dingle P, Stick S. Raised exhaled nitric oxide in healthy children is associated with domestic formaldehyde levels. Am J Respir Crit Care Med 2000; 161:1757–1759
175 Tozzi AE, Rava L, Ciofi degli Atti ML, et al. Clinical presentation of pertussis in unvaccinated and vaccinated children in the first six years of life. Pediatrics 2003; 112:1069–1075
176 Couriel J. Pnuemonia due to small bacterial organisms. In: Ellis M, ed. Infectious diseases of the respiratory tract. Cambridge, UK: Cambridge University Press, 1998; 222–236
177 Hallander HO, Gnarpe J, Gnarpe H, et al. *Bordetella pertussis*, *Bordetella parapertussis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and persistent cough in children. Scand J Infect Dis 1999; 31:281–286
178 Torvaldsen S, Simpson JM, McIntyre PB. Effectiveness of pertussis vaccination in New South Wales, Australia, 1996–1998. Eur J Epidemiol 2003; 18:63–69
179 Bianchetti MG, Caflisch M, Oetliker OH. Cough and converting enzyme inhibitors. Eur J Pediatr 1992; 151:225–226
180 von Vigier RO, Mozzettini S, Truttmann AC, et al. Cough is common in children prescribed converting enzyme inhibitors [letter]. Nephron 2000; 84:98
181 Rokicki W, Borowicka E. Use of converting angiotensin inhibitors in children: II. Personal experience with enalapril. Wiad Lek 1997; 50:85–93
182 Dubus JC, Mely L, Huiart L, et al. Cough after inhalation of corticosteroids delivered from spacer devices in children with asthma. Fundam Clin Pharmacol 2003; 17:627–631
183 Smyth MD, Tubbs RS, Bebin EM, et al. Complications of chronic vagus nerve stimulation for epilepsy in children. J Neurosurg 2003; 99:500–503
184 Wamboldt MZ, Wamboldt FS. Psychiatric aspects of respiratory syndromes. In: Taussig LM, Landau LI, eds. Pediatric respiratory medicine. St. Louis, MO: Mosby, 1999; 1222–1234
185 Tekdemir I, Aslan A, Elhan A. A clinico-anatomic study of the auricular branch of the vagus nerve and Arnold's ear-cough reflex. Surg Radiol Anat 1998; 20:253–257
186 Bloustine S, Langston L, Miller T. Ear-cough (Arnold's) reflex. Ann Otol Rhinol Laryngol 1976; 85:406–407
187 Todisco T. The oto-respiratory reflex. Respiration 1982; 43:354–358
188 Sheehy JL, Lee S. Chronic cough due to cholesteatoma. A case report. Am J Otol 1988; 9:392
189 Raman R. Impacted ear wax: a cause for unexplained cough [letter]? Arch Otolaryngol Head Neck Surg 1986; 112:679
190 Hammond RR, Ebers GC. Chronic cough following cardiac transplantation: vagal Mitempfindung? J Neurol Neurosurg Psychiatry 1992; 55:723–724
191 Smith FM Jr. Arnold's nerve reflex; a little known cause of cough in pediatric patients. J La State Med Soc 1963; 115:17–18
192 Jegoux F, Legent F, Beauvillain DM. Chronic cough and ear wax. Lancet 2002; 360:618
193 Cataneo AJ, Reibscheid SM, Ruiz Junior RL, et al. Foreign body in the tracheobronchial tree. Clin Pediatr (Phila) 1997; 36:701–706
194 Oguz F, Citak A, Unuvar E, et al. Airway foreign bodies in childhood. Int J Pediatr Otorhinolaryngol 2000; 52:11–16
195 Mu L, He P, Sun D. Inhalation of foreign bodies in Chinese children: a review of 400 cases. Laryngoscope 1991; 101:657–660
196 Raman TS, Mathew S, Ravikumar, et al. Atelectasis in children. Indian Pediatr 1998; 35:429–435
197 Butler CC, Kinnersley P, Hood K, et al. Clinical course of acute infection of the upper respiratory tract in children: cohort study. BMJ 2003; 327:1088–1089
198 Carr AJ, Gibson B, Robinson PG. Measuring quality of life: is quality of life determined by expectations or experience? BMJ 2001; 322:1240–1243
199 Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations questionnaire study. BMJ 1997; 315:520–523
200 Little P, Gould C, Williamson I, et al. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. BMJ 1997; 315:350–352
201 Dewey CR, Hawkins NS. The relationship between the treatment of cough during early infancy and maternal education level, age and number of other children in the household: ALSPAC Study Team; Avon Longitudinal Study of Pregnancy and Childhood. Child Care Health Dev 1998; 24:217–227
202 Mangione-Smith R, McGlynn EA, Elliott MN, et al. The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior. Pediatrics 1999; 103:711–718
203 Pandolfini C, Impicciatore P, Bonati M. Parents on the web: risks for quality management of cough in children. Pediatrics 2000; 105:e1
204 Cornford CS, Morgan M, Ridsdale L. Why do mothers consult when their children cough? Fam Pract 1993; 10:193–196
205 Davies MJ, Cane RS, Ranganathan SC, et al. Cough, wheeze and sleep [letter]. Arch Dis Child 1998; 79:465
206 Berlin CM, McCarver-May DG, Notterman DA, et al. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics 1997; 99:918–919
207 Gunn VL, Taha SH, Liebelt EL, et al. Toxicity of over-the-

counter cough and cold medications. Pediatrics 2001; 108: E52
208 Chien C, Marriott JL, Ashby K, et al. Unintentional ingestion of over the counter medications in children less than 5 years old. J Paediatr Child Health 2003; 39:264–269
209 Pillay V, Swingler G. Symptomatic treatment of the cough in whooping cough. Cochrane Database Syst Rev (database online). Issue 4; 2003
210 Smucny JJ, Flynn CA, Becker LA, et al. Are β_2-agonists effective treatment for acute bronchitis or acute cough in patients without underlying pulmonary disease? A systematic review. J Fam Pract 2001; 50:945–951
211 Chang AB, McKean M, Morris P. Inhaled anticholinergics for prolonged non-specific cough in children. Cochrane Database Syst Rev (database online). Issue 4; 2003
212 Creticos PS. Effects of nedocromil sodium on inflammation and symptoms in therapeutic studies. J Allergy Clin Immunol 1996; 98:S143–S149
213 Hiller EJ, Milner AD, Lenney W. Nebulized sodium cromoglycate in young asthmatic children: double-blind trial. Arch Dis Child 1977; 52:875–876
214 Yuksel B, Greenough A. The effect of sodium cromoglycate on upper and lower respiratory symptoms in children born prematurely. Eur J Pediatr 1993; 152:615–618
215 Chang AB, Marchant JM, Morris P. Cromones for prolonged non-specific cough in children. Cochrane Database Syst Rev (database online). Issue 1; 2004
216 Spelman R. Two-year follow up of the management of chronic or recurrent cough in children according to an asthma protocol. Br J Gen Pract 1991; 41:406–409
217 Yahav Y, Katznelson D, Benzaray S. Persistent cough: a forme-fruste of asthma. Eur J Respir Dis 1982; 63:43–46
218 Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1–5 years: randomised controlled trial. Lancet 2003; 362:1433–1438
219 Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003; 361:1071–1076
220 O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001; 164:1392–1397
221 Parameswaran K, O'Byrne PM, Sears MR. Inhaled corticosteroids for asthma: common clinical quandaries. J Asthma 2003; 40:107–118
222 Allen DB, Bielory L, Derendorf H, et al. Inhaled corticosteroids: past lessons and future issues. J Allergy Clin Immunol 2003; 112:S1–S40
223 Macdessi JS, Randell TL, Donaghue KC, et al. Adrenal crises in children treated with high-dose inhaled corticosteroids for asthma. Med J Aust 2003; 178:214–216
224 McFadden ER. Exertional dyspnea and cough as preludes to acute attacks of bronchial asthma. N Engl J Med 1975; 292:555–558
225 Gottfarb P, Brauner A. Children with persistent cough: outcome with treatment and role of *Moraxella catarrhalis*? Scand J Infect Dis 1994; 26:545–551
226 Darelid J, Lofgren S, Malmvall BE. Erythromycin treatment is beneficial for longstanding *Moraxella catarrhalis* associated cough in children. Scand J Infect Dis 1993; 25:323–329
227 Morris P, Leach A. Antibiotics for persistent nasal discharge (rhinosinusitis) in children. Cochrane Database Syst Rev (database online). Issue 2; 2002
228 Dowell SF, Schwartz B, Phillips WR. Appropriate use of antibiotics for URIs in children: part I. Otitis media and acute sinusitis; The Pediatric URI Consensus Team. Am Fam Physician 1998; 58:1113–1123
229 Arroll B, Kenealy T. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database Syst Rev (database online). Issue 3; 2002
230 De Sutter AIM, Lemiengre M, Campbell H, et al. Antihistamines for the common cold. Cochrane Database Syst Rev (database online). Issue 3; 2003
231 Orenstein SR, Shalaby TM, Putnam PE. Thickened feedings as a cause of increased coughing when used as therapy for gastroesophageal reflux in infants. J Pediatr 1992; 121:913–915
232 Vanderhoof JA, Moran JR, Harris CL, et al. Efficacy of a pre-thickened infant formula: a multicenter, double-blind, randomized, placebo-controlled parallel group trial in 104 infants with symptomatic gastroesophageal reflux. Clin Pediatr (Phila) 2003; 42:483–495
233 Dordal MT, Baltazar MA, Roca I, et al. [Nocturnal spasmodic cough in the infant: evolution after antireflux treatment. Allerg Immunol (Paris) 1994; 26:53–58
234 Ours TM, Richter JE. Re: Irwin editorial: cough and GERD. Am J Gastroenterol 2000; 95:1833–1836
235 Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. Am J Gastroenterol 1999; 94:3131–3138
236 Irwin RS, Richter JE. Gastroesophageal reflux and chronic cough. Am J Gastroenterol 2000; 95:S9–S14
237 Craig WR, Hanlon-Dearman A, Sinclair C, et al. Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years. Cochrane Database Syst Rev (database online). Issue 3; 2004
238 Rudolph CD. Supraesophageal complications of gastroesophageal reflux in children: challenges in diagnosis and treatment. Am J Med 2003; 115(suppl):150S–156S
239 Howaizi M, Delafosse C. Omeprazole-induced intractable cough. Ann Pharmacother 2003; 37:1607–1609
240 Committee on Substance Abuse. American Academy of Pediatrics: tobacco's toll: implications for the pediatrician. Pediatrics 2001; 107:794–798
241 Brand PL, Duiverman EJ. Coughing and wheezing children: improvement after parents stop smoking. Ned Tijdschr Geneeskd 1998; 142:825–827
242 Hovell MF, Zakarian JM, Matt GE, et al. Effect of counselling mothers on their children's exposure to environmental tobacco smoke: randomised controlled trial. BMJ 2000; 321:337–342
243 Somerville M, Mackenzie I, Owen P, et al. Housing and health: does installing heating in their homes improve the health of children with asthma? Public Health 2000; 114: 434–439
244 Fitzmaurice DA. Written information for treating minor illness. BMJ 2001; 322:1193–1194
245 Little P, Somerville J, Williamson I, et al. Randomised controlled trial of self management leaflets and booklets for minor illness provided by post. BMJ 2001; 322:1214
246 Taylor JA, Kwan-Gett TS, McMahon EM Jr. Effectiveness of an educational intervention in modifying parental attitudes about antibiotic usage in children. Pediatrics 2003; 111:e548–e554
247 Cherry JD. The treatment of croup: continued controversy due to failure of recognition of historic, ecologic, etiologic and clinical perspectives. J Pediatr 1979; 94:352–354
248 Kao NL, Richmond GW. Cough productive of casts. Ann Allergy Asthma Immunol 1996; 76:231–233
249 Weinberg EG. "Honking": Psychogenic cough tic in children. S Afr Med J 1980; 57:198–200

250 Jenkinson D. Natural course of 500 consecutive cases of whooping cough: a general practice population study. BMJ 1995; 310:299–302
251 Schaad UB, Rossi E. Infantile chlamydial pneumonia: a review based on 115 cases. Eur J Pediatr 1982; 138:105–109
252 Coren ME, Ng V, Rubens M, et al. The value of ultrafast computed tomography in the investigation of pediatric chest disease. Pediatr Pulmonol 1998; 26:389–395
253 Tatli MM, San I, Karaoglanoglu M. Paranasal sinus computed tomographic findings of children with chronic cough. Int J Pediatr Otorhinolaryngol 2001; 60:213–217
254 Diament MJ, Senac MO, Gilsanz V, et al. Prevalence of incidental paranasal sinuses opacification in pediatric patients: a CT study. J Comput Assist Tomogr 1987; 11:426–431
255 Kim CK, Kim JT, Kang H, et al. Sputum eosinophilia in cough-variant asthma as a predictor of the subsequent development of classic asthma. Clin Exp Allergy 2003; 33:1409–1414
256 Colombo JL, Hallberg TK. Recurrent aspiration in children: lipid-laden alveolar macrophage quantitation. Pediatr Pulmonol 1987; 3:86–89
257 Bauer ML, Lyrene RK. Chronic aspiration in children: evaluation of the lipid-laden macrophage index. Pediatr Pulmonol 1999; 28:94–100
258 Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. Pediatr Pulmonol 1999; 27:419–422
259 Kazachkov MY, Muhlebach MS, Livasy CA, et al. Lipid-laden macrophage index and inflammation in bronchoalveolar lavage fluids in children. Eur Respir J 2001; 18:790–795
260 Strauch E, Neupert T, Ihorst G, et al. Bronchial hyperresponsiveness to 4.5% hypertonic saline indicates a past history of asthma-like symptoms in children. Pediatr Pulmonol 2001; 31:44–50
261 Marchant JM, Masel JP, Dickinson FL, et al. Application of chest high-resolution computer tomography in young children with cystic fibrosis. Pediatr Pulmonol 2001; 31:24–29
262 Senzilet LD, Halperin SA, Spika JS, et al. Pertussis is a frequent cause of prolonged cough illness in adults and adolescents. Clin Infect Dis 2001; 32:1691–1697
263 Schmidt SM, Muller CE, Mahner B, et al. Prevalence, rate of persistence and respiratory tract symptoms of *Chlamydia pneumoniae* infection in 1211 kindergarten and school age children. Pediatr Infect Dis J 2002; 21:758–762
264 Liese JG, Renner C, Stojanov S, et al. Clinical and epidemiological picture of *B pertussis* and *B parapertussis* infections after introduction of acellular pertussis vaccines. Arch Dis Child 2003; 88:684–687
265 van Asperen PP, McKay KO, Mellis CM, et al. A multicentre randomized placebo-controlled double-blind study on the efficacy of Ketotifen in infants with chronic cough or wheeze. J Paediatr Child Health 1992; 28:442–446
266 Ciprandi G, Tosca M, Ricca V, et al. Cetirizine treatment of allergic cough in children with pollen allergy. Allergy 1997; 52:752–754
267 Hueston WJ. Antibiotics: neither cost effective nor "cough" effective. J Fam Pract 1997; 44:261–265
268 Chan PW, Debruyne JA. Inhaled nedocromil sodium for persistent cough in children. Med J Malaysia 2001; 56:408–413
269 Dalby-Payne JR, Morris AM, Craig JC. Meta-analysis of randomized controlled trials on the benefits and risks of using cisapride for the treatment of gastroesophageal reflux in children. J Gastroenterol Hepatol 2003; 18:196–202
270 Barlan IB, Erkan E, Bakir M, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Ann Allergy Asthma Immunol 1997; 78:598–601
271 Yilmaz G, Varan B, Yilmaz T, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Eur Arch Otorhinolaryngol 2000; 257: 256–259
272 Chang AB. Causes, assessment and measurement in children. In: Chung FK, Widdicombe JG, Boushey HA, eds. Cough: causes, mechanisms and therapy. London, UK: Blackwell Science, 2003; 57–73